The Evans-Tishchenko Reaction: Scope and Applications**

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[**] We thank Cancer Research UK (studentship to KJR) for financial support.

Graphical abstract:

Keywords:
Evans-Tishchenko reaction; anti-1,3-diols; diastereoselectivity; Lewis acids; samarium; natural products
Abstract

The Evans-Tishchenko reaction provides a highly diastereoselective route towards the synthesis of 1,3-anti diol monoesters, and therefore has found prominent use in a number of synthetic applications. This review summarizes recent applications of the Evans-Tishchenko reaction in natural product synthesis, and examines scope in terms of substrate range, functional group tolerance, and catalyst.

1. Introduction

The Tishchenko reaction was first described in 1906 and entails the Lewis acid mediated condensation of two molar equivalents of an aldehyde to form an ester (Scheme 1a). In 1990, Evans and Hoveyda reported an important variant of this reaction, which has subsequently become known as the Evans-Tishchenko reaction. This transformation involves a preformed β-hydroxyketone and an aldehyde undergoing a Lewis acid catalyzed condensation to generate a 1,3-anti diol monoester (Scheme 1b). Importantly, the Evans-Tishchenko reaction provides a highly regio- and diastereo-selective route to these ubiquitous structural units; and the reaction itself is remarkably mild and can be carried out in the presence of a number of (often sensitive) functional groups. The resultant 1,3-anti diol monoesters may be retained as a selectively protected diol; serve as a means of fragment coupling; or be readily transformed into other interesting structural motifs. These features have rendered the Evans-Tishchenko reaction a key step in a number of natural product syntheses.

Scheme 1. (a) Tishchenko, (b) Evans-Tishchenko and (c) aldol-Tishchenko Reactions.

This review discusses the scope of the Evans-Tishchenko reaction in terms of the range of catalysts/promoters and its functional group tolerance, and highlights the versatility of the reaction in terms of its application to natural product synthesis. The closely-related Tishchenko and aldol-Tishchenko (Scheme 1c) reactions are not covered, as both have been the subject of recent surveys.\(^3\,^4\)
2 Reaction Mechanism and Catalyst Scope

2.1 Reaction Mechanism

In the first reported Evans-Tishchenko reaction a samarium-based Lewis acid catalyst was generated \textit{in situ}; under these conditions 1,3-\textit{anti} diol monoesters were generated in excellent yield (>85%) and diastereoselectivity (>99:1).\textsuperscript{2} The mechanism proposed to explain this selectivity involves Lewis acid promoted hemiacetal formation (Scheme 2a), followed by intramolecular hydride transfer from the aldehyde to the newly formed carbinol centre \textit{via} a 6,6-chair-type transition state 1.\textsuperscript{2} The hydride transfer mechanism is supported by deuterium labeling studies in which \textit{d}_4-acetaldehyde 3 was shown to selectively label the carbon backbone at the newly-formed hydroxyl stereocentre (2 \rightarrow 4, Scheme 2b).\textsuperscript{2} Although the reaction is generally both very highly diastereoselective and regioselective, two common side-reactions are known. Where the Evans-Tishchenko reaction results in ester products which are sterically crowded, Lewis acid catalyzed transesterification between the two hydroxyl of the 1,3-\textit{anti} diol may occur (5 \rightarrow 6, Scheme 2c).\textsuperscript{5,6} In addition, there is often a delicate interplay with a second pathway in which an epimerisation/Evans-Tishchenko reaction,\textsuperscript{5,7} or alternatively a Lewis acid catalyzed retro-aldol/aldol-Tishchenko (RAAT) reaction takes place.\textsuperscript{8} This latter pathway may result in the scrambling of the \(\alpha\)-stereocentre, with the net generation of the thermodynamically favoured \textit{anti} aldol adduct with 1,3-\textit{anti} diol stereochemistry (9, Scheme 2d). The extent to which this pathway competes with the Evans-Tishchenko reaction depends upon the nature of the Lewis acid catalyst used, as discussed in the following sections.
Scheme 2. (a) General mechanism for the Evans-Tishchenko reaction. (b) $d_4$-Acetaldehyde labelling study. Common side-reactions: (c) transesterification; (d) (i) epimerisation/Evans-Tishchenko and (ii) retro-aldol/aldol-Tishchenko (RAAT).

2.2 Samarium

The first example of the Evans-Tishchenko reaction was reported by Evans and Hoveyda,$^2$ who utilized a catalytic quantity (15 mol%) of samarium diiodide in the presence of an excess of the reacting aldehyde to generate the active Lewis acid catalyst (Scheme 3a). It has since been suggested$^9$ that samarium-pinacol
species 12 [(RCHO)$_2$SmI•SmI$_3$] generated from reaction of samarium diiodide and either the reactive, or a sacrificial aldehyde, is responsible for catalysis (Scheme 3b). Typically quite high catalytic loadings of samarium diiodide are used (15-30 mol%), generating 7-15 mol% of the active species in situ. A survey of other samarium species has shown that samarium triiodide, samarium trichloride and Sm(acac)$_3$ are not effective catalysts for the reaction. The pinacolate Lewis acid generated from samarium diiodide and a reactive aldehyde is a widely-used catalyst for Evans-Tishchenko reactions, and most reactions in the following sections make use of catalysts of this type. Unfortunately, samarium diiodide is air- and moisture-sensitive, and although commercially available, a number of methods for generating samarium diiodide in situ have been developed to counter the inherent difficulties in long-term storage. Reacting an excess of metallic samarium with elemental iodine at elevated temperature, under ultrasonic vibration or through use of microwave irradiation in (typically) THF is sufficient to generate solutions of the precatalyst comparatively rapidly (<3 h) and on a gram scale for use in Evans-Tishchenko reactions, or alternative applications. Other iodide sources have also been used, including diiodomethane, iodoform, 1,2-diiodoethane, and sodium iodide/chlorotrimethylsilane but the low cost, improved atom economy and ready availability of elemental iodine have rendered these approaches less widespread. Despite the prominent use of samarium diiodide, a number of other metal catalysts have also been successfully been employed in Evans-Tishchenko coupling as discussed in the following sections.

![Scheme 3](image_url)

Scheme 3. (a) First example of the samarium-catalyzed Evans-Tishchenko reaction. (b) Generation of a catalytically active samarium(III) pinacolate, Lewis acid catalyst.
2.3 Scandium

Scandium triflate has been identified as a promising Lewis acid in organic synthesis,\textsuperscript{18} and has been shown to be effective in the Evans-Tishchenko reaction.\textsuperscript{19} The primary alcohol 13 was successfully converted to the Evans-Tishchenko product 14 in excellent yield (95%) in the presence of 10 mol% scandium triflate, albeit requiring slow addition (2.5 h) of the \( \beta \)-hydroxyketone to circumvent formation of acetal byproducts (e.g. 15, Scheme 4\textsuperscript{a}). Conversely, secondary alcohols 16 underwent Evans-Tishchenko reduction smoothly (without the necessity for careful addition) to give the corresponding 1,3-\textit{anti} diol monoesters 17 in moderate to excellent yield (17-93%) and diastereoselectivity (86:12 to >97:3 \textit{dr}). The main disadvantage of the protocol was the requirement for long reaction times (48 to 120 h) in contrast to the samarium pinacolate catalyzed reactions which are typically complete within a much shorter timeframe (20 min to 1 h). However, the reaction takes place under comparable conditions to samarium mediated protocols (\(-10 \textdegree C, \text{THF solvent}\)), avoids the use of a radioactive metal and carries other key advantages of air- and moisture-stability when compared to other protocols. Scandium triflate could therefore provide a useful alternative where stringently dry conditions are difficult to achieve, for example where crude samples of reactant aldehydes or \( \beta \)-hydroxyketones must be used without purification due to problems of instability.

\textbf{Scheme 4}. Scandium-based Lewis acid catalyzed Evans-Tishchenko reactions.

2.4 Zirconium

Zirconocene catalyst \( \text{Cp}_2\text{ZrH}_2 \) was the first zirconium Lewis acid to be used successfully in the Evans-Tishchenko reaction.\textsuperscript{20} Treatment of \( \beta \)-hydroxyketone 18 with 4 equivalents of alkyl aldehydes and a catalytic quantity (5 mol\%) of \( \text{Cp}_2\text{ZrH}_2 \) (Scheme 5\textsuperscript{a}) gave the corresponding 1,3-\textit{anti} diol monoesters 19 in good to excellent yields (55-98%). Interestingly, benzaldehyde and crotonaldehyde failed to react, a feature of the
reaction that was attributed to the electron-withdrawing effect of these groups which would impede transfer of the hydride to the carbonyl group.\textsuperscript{20} Furthermore, reaction of racemic $\alpha$-methyl $\beta$-hydroxyketone 20 led to excellent syn-selectivity (95:5 $dr$) in the product 22 (Scheme 5b). This was attributed to the presumed equatorial placement of the methyl group that would occur during the transition state 21, as opposed to axial placement which would give the anti-product.

The zirconium alkoxide Lewis acid, Zr(O′Bu)$_4$ has also been successfully employed as a catalyst for the Evans-Tishchenko reaction,\textsuperscript{7} and offers similar reactivity to samarium pinacolate catalysts for alkyl aldehydes which react smoothly to give the corresponding 1,3-anti diol monoester products 24 (Scheme 5c). The reaction is carried out in the presence of catalytic quantities of Zr(O′Bu)$_4$ (5-10 mol%) at low temperature (−30 °C) with an excess of the aldehyde (1.5-2.5 equivalents). But in contrast to most samarium-mediated protocols, the reaction is conducted in toluene.\textsuperscript{7} As with the zirconocene hydride based catalysts, aromatic and $\alpha,\beta$-unsaturated aldehydes yielded only trace amounts of products. In addition, when $\alpha$-substituted $\beta$-hydroxyketones were employed as substrates, substantial levels of epimerization at the $\alpha$-sterocentre were observed. This indicated that retro-aldol, or epimerization, reactions took place at a rate competitive with the desired Evans-Tishchenko reduction; and hence that the conditions were not suitable for the synthesis of polypropionate-derived 1,3-polyols.

\textbf{Scheme 5.} Zirconium-based Lewis acid catalysis of the Evans-Tishchenko reaction: (a) and (b) Cp$_2$ZrH$_2$; (c) Zr(O′Bu)$_4$.

\textbf{2.5 Other Metals}

Although they have not received very much attention, the use of hafnium-, magnesium- and ytterbium-based Lewis acid catalysts are worthy of mention as they have also shown activity in the Evans-Tishchenko reaction.
During their study of zirconium catalysts Schneider et al. showed that hafnium(IV) tert-butoxide and dibutyl magnesium showed high diastereoselectivity (>99:1 dr) and conversion (>77%) with similar activity to the zirconium catalyst, while yttrium(III) isopropoxide showed moderate activity as a catalyst in the Evans-Tishchenko reaction (51% yield, 90:10 dr) between isobutyraldehyde and β-hydroxyketone 25 (Scheme 6). Although only used in screening, it is clear that they have potential in future studies of the Evans-Tishchenko reaction, and indeed yttrium has already been employed in the related aldol-Tishchenko reaction. The success achieved with the use of magnesium-based catalysts is particularly noteworthy given the relatively low cost of magnesium when compared to expensive rare-Earth transition metals.

Scheme 6. Other metal mediated Evans-Tishchenko reactions.

3 Substrate Scope

The first samarium-catalyzed Evans-Tishchenko reaction2 made use of alkyl aldehydes and α-unsubstituted β-hydroxyketones (Scheme 3, above). However, sterically hindered substrates 27 and 29a also react smoothly to give their corresponding 1,3-anti diol monoesters (28 and 30 respectively), albeit requiring higher catalyst loadings (up to 40 mol% SmI2; Scheme 7ab). In contrast, no reaction was observed in the case of the benzyl ether 29b, even with a high catalyst loading (60 mol%). Presumably competitive chelation of the samarium catalyst by the benzyl ether inhibited the Evans-Tishchenko coupling, an effect which was also observed with an analogous p-methoxybenzyl ether in the total synthesis of (+)-croacin C.22 Surprisingly, oxazolidinone 31 also did not react as expected, leading to the formation of dioxalone 32. Curiously however, the very minor structural changes in oxazolidinone 33 allowed formation of the expected product 34, perhaps due to the shorter reaction time, subtle modulation of steric hindrance, or the enhanced nucleophilicity of the methoxy group vs. its isopropoxy counterpart (Scheme 7cd). In addition to alkyl and aryl substituents on the aldehyde, a range of electron rich heteroatom substituents have also been shown to react successfully. Smith et al.23 demonstrated that sulfur, phosphorus, silicon, selenium and tin containing aldehydes successfully couple to give 1,3-anti diol monoesters 35 (Scheme 8a). They also showed that a range of dithiane-containing esters 36 synthesized via the Evans-Tishchenko reaction could be converted using a number of different conditions.
(including base hydrolysis, rhodium/palladium catalysis and oxidative cleavage) to the corresponding carboxylic acid 37; thus providing a mild, albeit two-step, method of aldehyde oxidation which leaves the oxidation-sensitive thioacetal moiety intact (Scheme 8b).24

Scheme 7. Reaction of sterically hindered and polyketo β-hydroxyketones.

Scheme 8. (a) Coupling of a β-hydroxyketone and electron rich aldehydes in the Evans-Tishchenko reaction.
(b) Conversion of dithiane containing 1,3-anti diol monoesters to the corresponding carboxylic acid.
A number of studies have utilized alkyl and aryl aldehydes in the Evans-Tishchenko reaction (see Section 4), but heteroaryl aldehydes have also been shown to be good substrates. Research from our own laboratories recently demonstrated this using a number of electron-rich and electron-poor heteroaryl aldehydes (Scheme 9a). Electron-deficient aldehydes (for example, 3- and 4-formylpyridine) reacted with β-hydroxyketone 38 in the presence of comparatively low loadings of the samarium diiodide precatalyst (10 mol%), to give the corresponding 1,3-anti diol monoesters 39 in excellent yield (>93%) and diastereoselectivity (>90:10 dr) even at room temperature. Electron-rich heteroaryl aldehydes (for example furans and thiophenes) also gave high yields of the 1,3-anti diol monoesters (>95%), albeit requiring the presence of stoichiometric loadings of the samarium pinacolate species (derived from 200 mol% samarium diiodide precatalyst) and lower temperature coupling conditions to circumvent competitive RAAT side-reactions (38 → 40, Scheme 9b).

![Scheme 9](image)

**Scheme 9.** (a) Evans-Tishchenko coupling of heteroaryl aldehydes. (b) RAAT byproducts observed for electron-rich heteroaryl aldehydes with sub-stoichiometric loadings of the samarium catalyst.

The examples above demonstrate the use of α-unsubstituted and α-monosubstituted β-hydroxyketones in the Evans-Tishchenko reaction, combined with alkyl substitution on the distal side of the ketone functionality. However, relatively few examples exist of α,α-disubstituted systems; in their total synthesis of polycavernoside A, White et al. showed that gem-dimethyl substituents are tolerated, albeit leading to slightly diminished yields (45-60%) of the resulting 1,3-anti diol monoesters 42, (Scheme 10a). Only a catalytic quantity (15 mol%) of SmI₂ was required to effect the transformation, and a short reaction time (10 min) was used. Therefore despite obtaining only moderate yields, there is clearly scope for improvement of the conditions which would allow higher yields to be obtained. Conversely, excellent product yields have been obtained with α,β-unsaturated ketones. Kirschning et al. showed that β-hydroxyenone 43 reacted
successively in the Evans-Tishchenko reaction implying that conjugation is of little consequence in terms of reactivity (Scheme 10b). Indeed, the Evans-Tishchenko reaction, as demonstrated, is widely applicable and seldom fails even in the presence of a range of functionalities attached to each of the reactant carbon centres. A summary of the substrate scope as discussed in the current section is shown in Table 1.

Scheme 10. Evans-Tishchenko of (a) α,α-disubstituted β-hydroxyketones; and (b) a β-hydroxyenone.

<table>
<thead>
<tr>
<th>Group</th>
<th>Functionality Tolerated</th>
</tr>
</thead>
<tbody>
<tr>
<td>R¹</td>
<td>Alkyl, alkenyl, aryl; some O/N/Si² containing groups.</td>
</tr>
<tr>
<td>R²/R²’</td>
<td>H, alkyl.</td>
</tr>
<tr>
<td>R³</td>
<td>H, alkyl, alkenyl, alkynyl,* (some) benzyl, Br containing.*</td>
</tr>
<tr>
<td>R⁴</td>
<td>Alkyl, aryl, heteroaryl, N/O/P/S/Si containing.</td>
</tr>
</tbody>
</table>

*See examples in Section 4, below.

Table 1. Summary of viable substrates for the Evans-Tishchenko reaction.

4. Application in Natural Product Synthesis

Given that the Evans-Tishchenko reaction may be performed with a high degree of stereoselectivity on chiral β-hydroxyketones, and that it is tolerant of a wide range of functional groups, it is no surprise that it has found frequent application in natural product synthesis. The following section categorizes these reactions and details some recent uses of the Evans-Tishchenko reaction in the synthesis of natural products.
4.1. Protection/Asymmetric Induction

By far the most common use of the Evans-Tishchenko reaction is in tandem protection and asymmetric induction. There are a number of advantages associated with this strategy: first and foremost, a 1,3-anti diol is generated stereoselectively from the masked β-hydroxy ketone precursor; secondly, protection of the newly-formed hydroxyl group (e.g. as a silyl ether or benzyl ether) gives an orthogonally protected diol motif. Alternatively, esterification of the resulting 1,3-anti diol monoester lends itself to simultaneous hydrolytic deprotection at a later stage, which may help to streamline the total synthesis of such diol-containing natural products.

The synthesis of the macrolactone segment 47 of (+)-neopeltolide<sup>28</sup> provides an excellent example of the use of this strategy and indeed this approach has been used in at least three attempted syntheses of the cyclic core (Scheme 11a). In the first synthetic route,<sup>28a</sup> β- hydroxyketone 45a was reacted with benzaldehyde in the presence of SmI<sub>2</sub> to give the corresponding 1,3-anti diol monoester 46a (>20:1 dr). Critically, this gave the free alcohol, which allowed installation of the C(11) methoxy group present in the natural product, while simultaneously installing a benzoyl protecting group. An identical functional group pairing was introduced in the Hong’s<sup>28b</sup> total synthesis of the macrolactone 47, utilizing β-hydroxyketone 45b. In both cases, later removal of the benzoyl protecting group facilitated a key lactonisation and subsequent completion of the putative macrolactone core 47. In exploring the total synthesis of neopeltolide,<sup>28c</sup> Scheidt <i>et al.</i> also made use of an Evans-Tishchenko reaction to generate the C(11) methoxy group and provide a hydroxyl group for esterification to form key intermediate 52 (Scheme 11b). However, completion of the synthesis using this material revealed that this route provided a neopeltolide diastereomer 53 whose spectral data did not match the natural product. A second approach by this group, using the closely related monomethylated diol 55 generated the (11S,13S) stereochemistry and spectral data was found to match that of the natural product, leading to the reassignment of these stereocentres (Scheme 11c).
Scheme 11. Synthesis of (a) neopeltolide scaffold 53 using (i) 45a, PhCHO (6 eq), SmI$_2$ (50 mol%), THF, -10 °C, 5 h, 80%;$^{28a}$ or (ii) 45b, PhCHO (5 eq), SmI$_2$ (50 mol%), THF, 0 °C, 3 h, 87%;$^{28b}$ (b) (11R, 13R)-bisepineopeltolide 53; and (c) (+)-neopeltolide 56.

A SmI$_2$ mediated Evans-Tishchenko coupling was also employed in the stereoselective total synthesis of (+)-Rhizoxin D;$^{30}$ 1,3-anti diol formation followed by hydroxyl protection generated the fully protected C(10)-C(20) subunit (Scheme 12). In this case, p-nitrobenzaldehyde was coupled to the β-hydroxyketone 57 to generate the PNB (p-nitrobenzoyl) protected 1,3-diol 58 with a stoichiometric loading of SmI$_2$. Notably this particular Evans-Tishchenko reaction was performed in the absence of light: (a) to carefully control the reducing ability of SmI$_2$ (that can be enhanced in the presence of light);$^{30}$ and (b) to minimize the potential for reduction of the nitro functionality.$^{31}$ The reaction proceeded in excellent yield (86%) and subsequent protection of the free hydroxyl group as the silyl ether 59 allowed selective cleavage of the PNB group (DIBAL-H). Removal of the silyl group was carried out in the final step (HF/Pyridine) to generate the natural product 60.
Scheme 12. Evans-Tishchenko coupling in the synthesis of (+)-rhizoxin D.

The synthesis of the key C(1)-C(14) subunit 64 of (+)-discodermolide 65\textsuperscript{12} highlights another example of tandem-protection and asymmetric induction in natural product synthesis (Scheme 13). In this synthetic sequence, coupling of a propargylic β-hydroxyketone 61 with sacrificial propionaldehyde gave the corresponding 1,3-anti diol monoester 62 in excellent yield (95%) and, critically, allowed subsequent selective migration of the PMP acetal protecting group to the syn-related C(3) and C(5) hydroxyl groups (62 → 63, Scheme 13). This sequence demonstrated both the compatibility of the Evans-Tishchenko reaction with various functional groups (silyl ethers, a hindered PMP group, alkyne and alkenes) and its effectiveness at maintaining the stereochemical integrity of neighbouring chiral centres. Completion of the C(1)-C(14) subunit 64 was achieved in 6 steps; and (+)-discodermolide was synthesized in a further 7 steps by coupling with fragment 66 and subsequent protecting group cleavage.

Although the use of protecting groups has become commonplace in organic synthesis, they are often criticized for their low atom economy and the increased cost and synthetic complexity which they impart.\textsuperscript{33} However, deprotection strategies where multiple groups are removed simultaneously can help to reduce these disadvantages somewhat and provide a more streamlined route to the synthesis of polyols. In this context, the most obvious choice of dual protection would be to convert the hydroxyl formed as a result of the Evans-Tishchenko reaction to an ester, thus generating a 1,3-\textit{anti} diol diester. However, this strategy does not appear to have been adopted, most probably due to the comparative instability of the resultant diester and the lack of orthogonality with other deprotection strategies required for complex natural product synthesis. However, silyl protecting groups have been used in at least two studies, and these demonstrate that there is potential for the use of the Evans-Tishchenko reaction as part of an simultaneous deprotection strategy.

In pursuing the synthesis of the macrocyclic core \textbf{71} of leiodermatolide\textsuperscript{34} \textbf{72} the Paterson group used such a simultaneous deprotection strategy, hoping to achieve subsequent regioselective generation of the C(7)/C(9) β-hydroxycarbamate motif (\textbf{Scheme 14}). An initial Sml\textsubscript{2} mediated Evans-Tishchenko coupling of \textbf{67} with sacrificial propionaldehyde (>20:1 \textit{dr}), followed by basic workup (K\textsubscript{2}CO\textsubscript{3}) to facilitate ester cleavage, and TBS-protection of the resulting diol \textbf{68} gave the \textit{bis}-silyl ether \textbf{69}. Simultaneous deprotection of both hydroxyls with HF/pyridine to reveal the diol \textbf{70} was performed 9 steps later, during which time the chirality was preserved through two periodinane-mediated oxidations and two Grignard additions. The synthesis of the macrocycle \textbf{71} was successfully completed in 7 steps from this diol \textbf{70}.

\textbf{Scheme 14}. Simultaneous diol deprotection in the synthesis of leiodermatolide.
A second example of streamlined deprotection facilitated by the conversion of the ester resulting from an Evans-Tishchenko reaction to a silyl protecting group has been reported in the synthesis of the altohytrin A CD-spiroacetal subunit 77 (Scheme 15). Reaction of 73 with sacrificial propionaldehyde, followed by methylation of the free alcohol generated methyl ether 74. Exchange of the propionate ester for a silyl ether was found to be facile (91% over 2 steps), and conversion of the C(23) benzyl-protected alcohol to a ketone gave the substrate for a key boron mediated acetate aldol reaction which generated the linear C(16)-C(28) fragment 75 with excellent diastereoselectivity (>97:3 dr). Simultaneous deprotection of the C(19) and C(27) hydroxyls of 75 with HF/pyridine led to spiroketal formation albeit with poor selectivity (1:5) for the desired spiroketal 76b. Fortunately, the reaction proceeded in excellent yield (88%) and the diastereoisomers were readily equilibrated (HCl) to give a 1:1 mixture of the two isomers 76, which were easily separated by chromatography thus providing a reliable route to the altohytrin A CD-spiroacetal subunit 77.

Scheme 15. Simultaneous deprotection in the synthesis of the altohytrin CD-spirocyclic subunit.

4.2 Functional Group Interconversion

As highlighted in Section 3 the Evans-Tishchenko reaction can be used as a two-step oxidation protocol. Although it is perhaps a more costly and less atom economical method when compared to standard protocols, its use can circumvent problems of substrate sensitivity. An example of such an Evans-Tishchenko oxidation process was published in the synthesis of (+)-13-deoxytedanolide (Scheme 16). In this synthetic
sequence, oxidation of the alcohol 77 to a carboxylic acid was required in the presence of both a number of double bonds and the oxidation-sensitive dithiane moiety. Model studies had shown that a number of standard oxidants including Dess-Martin Periodinane, TPAP/NMO and PCC led to decomposition or over-oxidation of the dithiane. However, following oxidation of alcohol 77 to the aldehyde, the Evans-Tishchenko reaction with a sacrificial β-hydroxyketone furnished the corresponding ester 78. Despite the need to use the intermediate aldehyde in an unpurified form (due to its instability), this example of the samarium-mediated Evans-Tishchenko reaction still gave a good yield of the desired product 78 (78%) for the two steps. Acetal deprotection and subsequent hydrolysis of the ester functionality furnished the Yamaguchi lactonisation precursor, seco-acid 79, which provided access to the desired natural product 80 in a further 10 steps.

Scheme 16. Use of the Evans-Tishchenko reaction as a mild oxidation in the synthesis of (+)-13-deoxytedanolide 80. Reagents and conditions: (i) SO₃•Py, DMSO; (ii) ROH (1 eq), SmI₂ (35 mol%), THF, –10 – 0 °C, absence of light, 78% yield over 2 steps.

An obvious transformation that may be required by synthetic chemists tackling a complex natural product synthesis is the ability to switch the positions of the alcohol and ketone groups in a β-hydroxyketone with a high degree of stereoselectivity. This can be achieved through use of the Evans-Tishchenko reaction, albeit requiring a multi-step process; an example of such a transformation is seen in the first total synthesis of the polyketide (−)-baconipyrene 85 (Scheme 17). Sacrificial acetaldehyde was used to generate the ester 82 from β-hydroxyketone 81 under samarium-catalyzed Evans-Tishchenko conditions. PMB protection of the resulting alcohol gave ether 83 which, after silyl ether deprotection of the primary alcohol, was subjected to
base-mediated ester cleavage and Swern oxidation to the corresponding keto-aldehyde 84. Although this β-hydroxyl to ketone switch takes place with inversion of the sense of hydroxyl stereochemistry, the inclusion of a Mitsunobu reaction could potentially generate the fully reversed β-hydroxyketone, and indeed this approach is discussed in the remainder of this sub-section.

**Scheme 17.** Inversion of hydroxyl and ketone groups in the total synthesis of (−)-baconipyrene 85.

Perhaps as important as inverting the functionality in a β-hydroxyketone, is reversal of stereochemistry in the diol diastereomer generated. This is made possible using the Evans-Tishchenko reaction by exploiting the differing reactivity of the resulting ester and hydroxyl groups; as demonstrated in the synthesis of battzeladine F. Following Evans-Tishchenko coupling of 86 with propanal (Scheme 18), a Mitsunobu reaction with hydrazoic acid was used to generate the corresponding azide 88 from the alcohol functionality. After liberation of the hydroxyl group from the ester, a second Mitsunobu reaction (with 4-nitrobenzoic acid) led to reversal of the enantiomeric configuration of the stereocentres while providing a straightforward means of later generating the free amino-alcohol 90. This was critical in the synthesis of the key C(22)-C(29) guanidinium ring system 91, which was converted stepwise to the desired product 92 (Scheme 18).
Scheme 18. Use of the Evans-Tishchenko reaction and functional group interconversions in the synthesis of battzelladine F 92.

4.3. Fragment Linkage and Ring Formation

Linking small, easily synthesized fragments to form part of a larger framework of a natural product is a strategy that is commonplace and almost universally carried out in modern organic syntheses. For this convergent approach to work effectively a high-yielding, selective and reliable reaction is required to bring the components together and hence reactions such as palladium catalyzed couplings are often employed. The ability to construct rings efficiently also plays an essential role in natural product synthesis. The Evans-Tishchenko reaction has also been used in both these types of transformation, albeit in a somewhat limited capacity.

The first reported Evans-Tishchenko reaction in natural product synthesis was that used in the total synthesis of (−)-rapamycin.41 The retrosynthesis included a SmI₂ mediated Evans-Tishchenko coupling between β-hydroxyketone 94 and the Boc-protected piperidine aldehyde 95 (Scheme 19). This reaction proceeded smoothly with 30 mol% of the preformed (PhCHO)₂SmI₃ pinacolate catalyst [formed by treatment of sacrificial benzaldehyde (0.6 eq relative to 94) with SmI₂ (66 mol%, relative to 94)] to give the corresponding 1,3-anti diol monoester 96 in excellent yield (95%) and diastereoselectivity (20:1 dr). Later chain extension, deprotection and cyclisation of the linear monomer gave the natural product 93. Aside from playing a key role...
in the synthesis of the desired product, this reaction demonstrated the potential of the Evans-Tishchenko reaction in fragment linkage; with successful SmI$_2$ mediated coupling taking place in the presence of a number of protecting groups, ether linkages, a double bond and the pipiridine nitrogen atom.

Scheme 19. Use of the Evans-Tishchenko reaction in the synthesis of (−)-rapamycin 93.

The use of the Evans-Tishchenko reaction in the formation of macrolactone rings is one which has been explored with varying degrees of success. Two possible approaches to the synthesis of macrolactones using this methodology are: i. an intramolecular Evans-Tishchenko reaction to form the lactone directly; or ii. an initial Evans-Tishchenko esterification followed by ring-closure to give the desired macrolactone through the use of orthogonal chemistry e.g. ring closing metathesis. The high diastereoselectivity imparted by the Evans-Tishchenko reaction combined with typically high yields and the fact that the reaction only reveals the second, potentially competing, hydroxyl during the reaction process makes this approach to macrolactone synthesis very attractive in complex natural product synthesis.

The first intramolecular Evans-Tishchenko reaction was carried out in model studies aimed at the synthesis of the cytotoxic marine natural product octalactin A. Octalactin A 97 contains a medium lactone ring (8-membered) which has proven difficult to cyclise under standard conditions (e.g. macrolactonisation under high dilution). Treatment of model cyclisation precursor 98 (Scheme 20a), which contains both aldehyde and β-hydroxyenone functionalities, with 30 mol% of a pre-formed pinacolate samarium catalyst at 0 °C led to formation of the 8-membered ring lactone 99, albeit in poor yield (30%). Unfortunately, the generation of a 1:1 mixture of diastereomers rendered the route non-viable for construction of octalactin A 97. However, NMR studies showed that this diastereomeric mixture arose from epimerisation of the C(8) methyl group due to the comparative instability of the β-hydroxyenone under the extended reaction times required for closure of a disfavoured medium ring, rather than low selectivity in the Evans-Tishchenko reaction. Therefore, the
intramolecular Evans-Tishchenko reaction remains a potentially useful, highly diastereoselective alternative to more traditional means of lactonisation.

Scheme 20. (a) Intramolecular Evans-Tishchenko reaction; and (b) Evans-Tishchenko ring-closing metathesis approach toward the synthesis of octalactin A. 97. (i) PhCHO (0.5 eq), SmI$_2$ (61 mol%), THF, 0 °C, 30 min; (ii) 101 (2 eq), 30 min; (iii) 100, 30 min.

Fortunately, a number of methods exist for the generation of medium sized rings, and the combination of the Evans-Tishchenko reaction with ring-closing metathesis provides a useful route to the synthesis of such lactones. The Hulme group 43 demonstrated this approach in a later synthesis of the 8-membered lactone core of octalactin A (Scheme 20b). Evans-Tishchenko coupling of β-hydroxyenone 100 with the aldehyde 101 (itself bearing an alkene functionality) provided the required metathesis precursor 102. Ring-closing metathesis under Fürstner's modified conditions 44 (to circumvent deleterious side-reactions caused by internal chelation of the metallocarbene) allowed the successful generation of key lactone 103 and provided a straightforward two-step approach to the synthesis of the ring system. Indeed, the highly convergent nature of this approach allowed intermediate 103 to be generated in only 8 steps longest linear sequence providing a promising route to the synthesis of octalactin A.
A second class of ring that has been constructed from the products of an Evans-Tishchenko reaction is the tetrahydropyran motif. Pyran-type systems may be readily accessed through stereoselective reaction of the hydroxyl group formed in the Evans-Tishchenko reaction with an appropriate electrophilic sink. This synthetic strategy was exploited in the Paterson group synthesis of the C(20)-C(32) subunit 109 of phorboxazole A 104. A cis-tetrahydropyran ring system was introduced through use of the Evans-Tishchenko reaction to generate the key hydroxyster 106, which could be converted to Weinreb amide 107 in 4 steps (Scheme 21). Ester-to-alcohol reduction and concomitant amide partial reduction to the intermediate δ-hydroxyenal 108 using an excess (7 eq) of Dibal-H gave the required donor (hydroxyl group) and acceptor (enal) moieties for an intramolecular Michael reaction. This was realised through straightforward acidic aqueous work-up to give a high yield (74%) and diastereoselectivity (89:11 dr) of the product tetrahydropyran. Key to this process was the Evans-Tishchenko reaction which formed the 1,3-anti diol monoester in high dr, allowed selective protection of the hydroxyl group with a bulky TBS ether to aid subsequent selective cis-pyran ring formation, and provided an ester which could be readily deprotected under orthogonal conditions to generate the Michael donor moiety. Although the total synthesis of phorboxazole A was not completed using this methodology, it provides an outstanding example of the versatility of the 1,3-anti diol monoester products generated via the Evans-Tishchenko reaction. 

5. Future Perspectives

Since the Evans-Tishchenko reaction was first published in 1990, it has proved to be an important tool in the stereoselective generation of 1,3-anti diols and their derivatives. The reaction, in particular when performed in the presence of Lewis acidic catalysts derived from samarium diiodide, has already shown remarkable tolerance in terms of substrate scope and has been successfully demonstrated with a range of electron-rich, electron-poor and sterically hindered substrates. These attributes, as well as the versatility of the resulting 1,3-anti diol monoesters, have proved invaluable in the synthesis of natural products.

Future work in the development of the Evans-Tishchenko reaction should focus on the use of alternative Lewis acid catalysts. These must be less expensive and/or more readily handled on large scale than current samarium diiodide based methodologies. A number of alternative catalysts have been used in the related aldol-Tishchenko reaction; these include lithium, lanthanum, titanium, yttrium and ytterbium. As the second step in the aldol-Tishchenko reaction is believed to have a similar transition state to the Evans-Tishchenko reaction, these metals would be worthy of study in efforts to identify those which can successfully catalyze the coupling of aldehydes and β-hydroxyketones without accompanying retro-aldol aldol-Tishchenko (RAAT) or epimerization aldol-Tishchenko reactions (c.f. Section 2.1). Although the use of inexpensive main group metals and transition metals such as iron, copper and zinc remain an ideal goal, much work is required in order to identify a catalyst or promoter which is as effective or offers other advantages or attributes over the samarium diiodide protocol.

The development of a widely-applicable asymmetric variant of the Evans-Tishchenko reaction would also be an extremely important advance in the field. To date only a very limited number of examples of this kind of transformation have been published. Chiral lithium binaphtholates have recently been shown to convert achiral β-hydroxyketones to the corresponding chiral 1,3-diol monoesters (Scheme 22). Thus reaction of terminal β-hydroxyketones 112 with benzaldehyde or pivaldehyde in the presence of 10 mol% of the lithium binaphtholate catalyst 111 (generated in situ from 110) led to the corresponding products 113 in generally excellent yields (64-96%) and enantioselectivities (>83 %ee). In some instances this product was accompanied by the undesired transesterification product 114 (c.f. Section 2.1). One example of the kinetic resolution of a racemic α-methyl-β-hydroxyketone 115 with the lithium binaphtholate catalyst 111 was also reported by Nakajima et al. Although attractive, these methods for the stereoselective generation of 1,3-diol monoesters and kinetic resolution of racemic α-substituted-β-hydroxyketones clearly lack generality and a greater understanding of both the reaction mechanism and substrate scope, are required before they can be widely adopted.
Scheme 22. (a) Generation of the lithium binaphtholate catalyst 111. Lithium mediated (b) asymmetric Evans-Tishchenko reactions; and (c) Evans-Tishchenko kinetic resolution.

In addition to the use of chiral BINOL-type ligands to induce asymmetry, a further intriguing possibility has been raised by recent reports of nickel catalysts with NHC ligands for related crossed-Tishchenko reactions. Under these conditions crossed alkanoate-benzyl esters 118 are selectively generated from the corresponding alkyl and aryl aldehydes (Scheme 23). Some mechanistic details of the reaction have been determined, but the extension of this catalytic system to the Evans-Tishchenko reaction, and the possibility of using chiral NHC ligands have yet to be explored.

Scheme 23. Nickel-catalyzed Tishchenko reaction.
To date, the Evans-Tishchenko reaction has predominantly been used in the construction of polyketides or the polyketide portion of mixed polyketide-NRPS natural products. However, when used in tandem with the Mitsunobu reaction (as demonstrated in the synthesis of battzeladine F\textsuperscript{40} in \textbf{Section 4.2}) the reaction provides an excellent means of introducing a number of functional groups, including nitrogen, stereoselectively. Hence in future a wider range of applications to include other natural product target classes might be expected. In addition, an intra- or inter-molecular Mitsunobu reaction with an acidic group following Evans-Tishchenko coupling would also provide an interesting, straightforward general method of generating lactones and other oxygen or nitrogen containing ring systems.\textsuperscript{52} Finally, substrate expansion to encompass the use of β-hydroxy imines is another unexplored area for the Evans-Tishchenko reaction; if suitable conditions were found this could add a complementary approach to the \textit{anti}-specific reduction of β-hydroxy-N-sulfinyl imines reported by Ellman et al.\textsuperscript{53}

It is clear that the generation of medium- and large-ring lactones using the intramolecular Evans-Tishchenko reaction remains an underdeveloped area of research. Similarly, further examples of Evans-Tishchenko reactions between alkene- or alkyne-containing aldehydes and alkenyl- or alkynyl-substituted β-hydroxyketones followed by ring-closing metathesis as a high yielding and highly diastereoselective route to unsaturated ring systems might be anticipated. In this review we have highlighted instances of the use of the Evans-Tishchenko reaction as a method of fragment linkage (\textbf{Section 4.3}). However, this strategy is still underutilized when compared with, for example, palladium catalyzed coupling reactions; this is especially surprising considering the relative ease of synthesis of both the reactive partners. Given that the 1,3-diol monoester, and related 1,3-derivatives are commonplace, and the Evans-Tishchenko reaction is particularly mild and tolerant of functionality, more syntheses could be built around an application of the Evans-Tishchenko reaction to join fragments in large natural products.

\textbf{6 Conclusion}

The Evans-Tishchenko reaction provides a reliable, mild, versatile and highly diastereoselective method of generating 1,3-\textit{anti} diol monoesters and will continue to find application in the synthesis of natural products and other biologically relevant structures. Future work should focus on the development of cheaper alternative catalysts (metal, organocatalysts etc.), asymmetric induction and kinetic resolution, extension of the substrate scope (e.g. to encompass β-hydroxythioketones/imines, β-thio/aminoketones) and the use of synthetic plans which exploit the enormous potential of the 1,3-\textit{anti} diol monoesters which result from the Evans-Tishchenko reaction.
References


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