Formal total synthesis of triptolide†

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A new approach to the medicinally-important natural product triptolide is significantly shorter than previous syntheses, highly convergent and avoids the use of protecting groups; key features include two Diels–Alder reactions and a new deoxygenative aromatisation process.

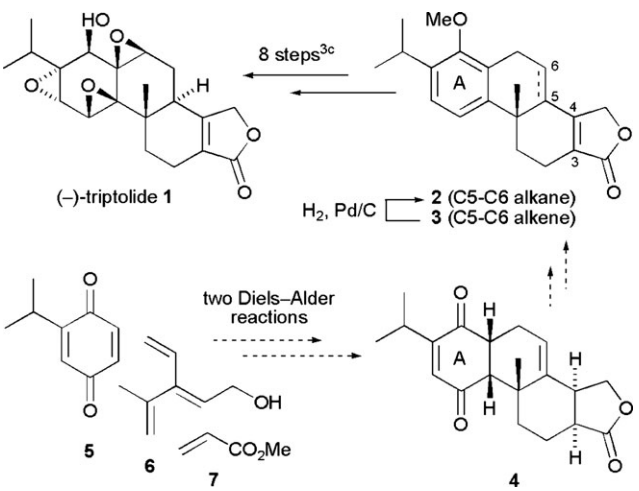
The isolation of triptolide (**1**) from the Asian vine *Tripterygium wilfordii* Hook F was first reported by Kupchan *et al*. in 1972.[1] Plants in this genus have a long history of use in traditional Chinese medicine. *Tripterygium* extracts—along with **1**, the main bioactive constituent—display potent anti-leukemic and anti-tumour properties, anti-inflammatory and immunosuppressive activities, and show potential as a male contraceptive.[2]

Diterpenoid triepoxide natural product **1** has been the focus of important synthetic endeavours by Berchtold,[3] van Tamelen[4] and Yang.[5] The first total synthesis by Berchtold involved the construction of tetracycle **2** over 20 steps from a tetralone precursor, followed by elaboration to **1** in 8 steps. Later approaches drew upon the pioneering efforts of Berchtold *et al*. in their conversion of **2**/**3** into **1**, and differ in their approach to tetracycles **2**/**3**. The most efficient of van Tamelen's three syntheses generates Berchtold's tetracycle **2** in 13 steps, the key step involving an elegant biomimetic cationic bicyclisation of a substituted benzene. Yang's approach assembles **2**through a 13 step route, involving an oxidative radical bicyclisation of a similar precursor, carrying a chiral auxiliary.

The significant current interest in the medicinal value of **1**[6] prompted our own synthetic approach to this important target. We envisaged the rapid assembly of tetracycle **4** by way of a diene-transmissive double Diels–Alder sequence of a substituted [3]dendralene,[7] such as **6** (Scheme 1). Aromatisation of ring A and incorporation of the C3=C4 olefin would lead to **3**, the advanced intermediate used in previous syntheses of **1**.[3c] In addition to its brevity, we were attracted to this route for two other reasons. Firstly, in principle, its convergent nature would facilitate the synthesis of analogues, and secondly, a successful cycloaddition with a chiral catalyst would constitute the first formal catalytic enantioselective total synthesis of triptolide.

The initial synthetic target was disubstituted [3]dendralene **6**, which we thought would be readily accessible through two successive C–C couplings of known dibromide **8**[8] with vinyl- and isopropenyl metal partners to give **10*E***, deprotection of which would give **6** (Scheme 2). As expected, 1,1-dibromoalkene **8** underwent highly stereoselective Stille or Negishi couplings to furnish either *Z*-bromodiene **9**[8] or **11**.

2-Bromo-1,3-dienes such as these have been shown to undergo smooth inversion of alkene geometry during coupling reactions.[7,9] Frustratingly, mixtures of the desired dendralene **10*E*** and its stereoisomer **10*Z*** were obtained from either **9** or **11** under all the conditions we examined (Table 1). Interestingly, whereas precursor **9** gives a 50 : 50 ratio of trienes **10*E*** and **10*Z*** under Pd(0) coupling conditions involving both Ph_3P[7] and *t*-Bu_3P[10] ligands, precursor **11** is selective for the retention product with Ph_3P and the inversion product with *t*-Bu_3P. Evidently, the stereoselectivity of this reaction is rather sensitive to both catalyst system and substrate. Following deprotection of the silyl ether, **6** underwent a regio- and *endo*-selective Diels–Alder reaction with methyl acrylate (**7**), which proceeded with concomitant lactonisation to give bicycle **12**, the projected precursor of tetracycle **4**. Low yields and poor stereocontrol in the formation of **10*E*** prompted us to develop an alternative route to semicyclic diene **12**. We reasoned that performing the Diels–Alder reaction prior to the incorporation of the vinyl group would circumvent issues of



Scheme 1 The double Diels–Alder approach to triptolide.

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† Electronic supplementary information (ESI) available: Chiral GC traces of enantioselective Diels–Alder reactions, and ^1H and ^{13}C NMR spectra for key compounds. Full experimental procedures, X-ray crystallographic data and anisotropic displacement ellipsoid plots for compounds **4**, **S5** (intermediate compound) and **15–17**; CCDC 658577 (**4**), 658578 (orthorhombic form of **S5**), 669352 (monoclinic form of **S5**) and 658574–658576 (**15–17**, respectively). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b718754h

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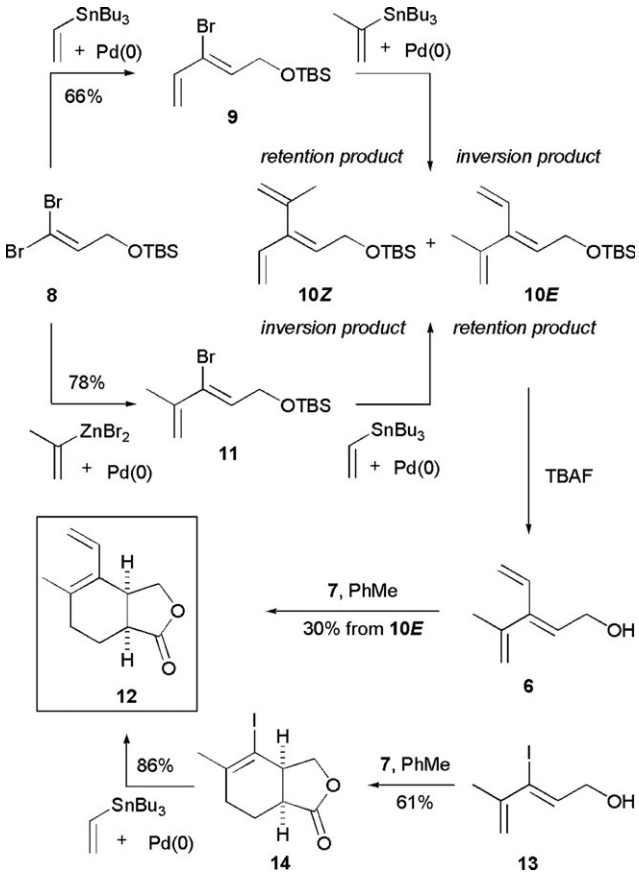


Scheme 2 Synthesis of semicyclic diene **12** (see Table 1 for product ratios and yields of the compound **10** stereoisomers).

stereoselection in the coupling reaction. Thus, known iodide **13**[11] underwent smooth intermolecular cycloaddition–lactonisation with **7**, and the resulting iodocyclohexene **14** underwent a high yielding Stille coupling with tributylvinylstannane under Farina conditions.[12]

With an efficient route to semicyclic diene **12** in hand, we examined the second Diels–Alder reaction in the sequence, which involves the union of **12** and 2-isopropyl-1,4-benzoquinone (**5**).[13] We anticipated an *endo*-mode dienophile approach to the convex α-face of the *cis*-fused bicycle, but this would merely control the stereochemistry of the reaction. The correct placement of the isopropyl substituent in the tetracyclic product **4** also necessitates the control of two regiochemical facets of the process. Firstly, cycloaddition must occur at the less substituted dienophile, and moreover, docking must proceed such that the isopropyl group resides proximate to the less substituted diene terminus. Gratifyingly, under high pressure conditions, diene **12** and dienophile **5** united to form two isomeric cycloadducts in an 83 : 17 ratio, the major product of which was the desired diastereomer **4** (Scheme 3).[14] A regio- and stereoselective reduction of the less hindered ketone delivered the C-14 α-hydroxy derivative, which was converted smoothly into the corresponding methyl ether **15**. We were delighted to discover that treatment of this compound with triflic anhydride in the presence of a sterically hindered base promoted C-11 deoxygenation and concomitant A-ring aromatisation to furnish **16** in 44% yield. A minor product isolated from this reaction was pentacycle **17**, the result of extensive rearrangements about the B/C ring system. The mechanism of these remarkable transformations presumably involves a common dienol triflate intermediate.[15] Completion of the formal total synthesis of (±)-triptolide required the conversion of saturated lactone **16** into butenolide **3**, a transformation which was readily accomplished through elimination of the selenoxide derivative.[16]

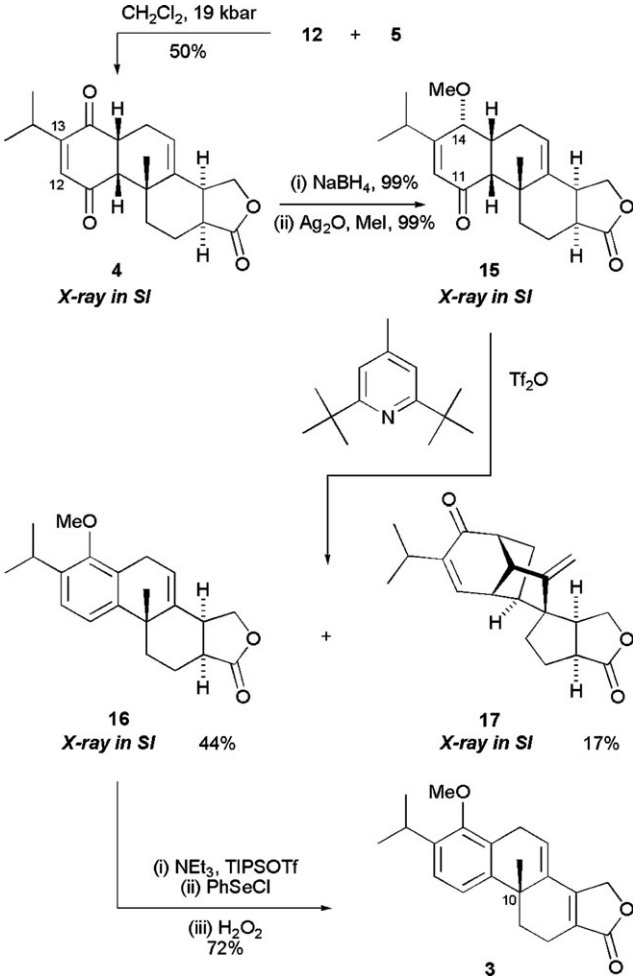
Following the successful completion of a formal total synthesis of (±)-triptolide, we turned our attention to the development of an enantioselective synthesis. An enantioselective transformation of iododienol **13** into *cis*-bicycle **14** was needed, since the stereogenicity of this compound is relayed into the C-10 quaternary stereocentre of target **3** through a highly diastereoselective second cycloaddition event (*i.e.*, **12** + **5** → **4** →→ **3**, Scheme 3). After considerable experimentation,[17] we were very pleased to find that Mikami's catalyst[18] promotes an efficient enantioselective Diels–Alder reaction between **13** and **7** (Table 2).[19] Very high enantioselectivities were obtained with a stoichiometric amount of the binol/$Cl_2Ti(O\textit{i}\text{-}Pr)_2$-derived Lewis acid (Table 2, entries 1 and 2), and acceptable levels of enantioselection were also recorded with relatively low catalyst loadings (Table 2, entry 3). It is generally accepted that higher enantioselectivities in reactions involving Mikami's catalyst are obtained by pre-mixing the binol and $Cl_2Ti(O\textit{i}\text{-}Pr)_2$ in the presence of powdered molecular sieves, then removing the sieves prior to addition of the substrate.[18,20] It is noteworthy that high yields and high enantioselectivities in the Diels–Alder reaction between **13** and **7** were obtained without the addition of molecular sieves at any stage (Table 2, entry 2).

In summary, a concise synthesis of Berchtold's tetracycle **3**—an advanced intermediate in several previous syntheses of triptolide—has been achieved. The successful sequence involves two intermolecular Diels–Alder reactions and avoids the use of protecting groups. The synthesis has been rendered enantioselective through promotion of the first cycloaddition event with Mikami's (binol)$TiCl_2$ catalyst. Along the way, new information pertaining to the coupling reactions of 2-bromo-1,3-dienes has been uncovered, and an intriguing deoxygenative aromatisation reaction has been developed. This new short route to triptolide is conceptually equivalent to a three

Table 1 Formation of **10** from precursors **9** and **11**[a]

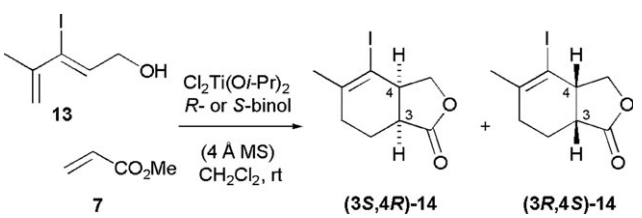
Precursor	Reactants	Ratio **10*Z*** : **10*E***	Yield (%)
9	$H_2C{=}C(CH_3)SnBu_3$, PPh_3, $Pd(OAc)_2$	50 : 50	49
9	$H_2C{=}C(CH_3)SnBu_3$, CsF, CuI, $PdCl_2$, *t*-Bu_3P	50 : 50	44
11	$H_2C{=}CHSnBu_3$, CsF, CuI, $PdCl_2$, *t*-Bu_3P	91 : 9	69
11	$H_2C{=}CHSnBu_3$, PPh_3, $Pd(OAc)_2$	28 : 72	46

[a] See Scheme 2.



Scheme 3 Synthesis of tetracycle **3** and completion of the formal total synthesis of **1**.

Table 2 Enantioselective synthesis of **14**



Entry	Binol/equiv.	4 Å MS	Time/h	Yield (%)	er[a]
1	*S*/1.0	Yes	48	75	3 : 97
2	*R*/1.0	No	48	89	97 : 3
3	*R*/0.1	Yes	72	91	89 : 11

[a] Enantiomer ratio (er) measured by chiral GC analysis.

component coupling process (Scheme 1). As such, families of structurally-related triptolide analogues should now be within reach.

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