Transannular Diels−Alder Entry into Stemodanes: First Asymmetric Total Synthesis of (+)-Maritimol

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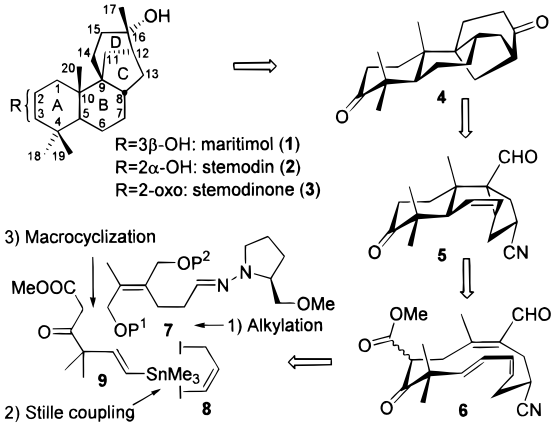
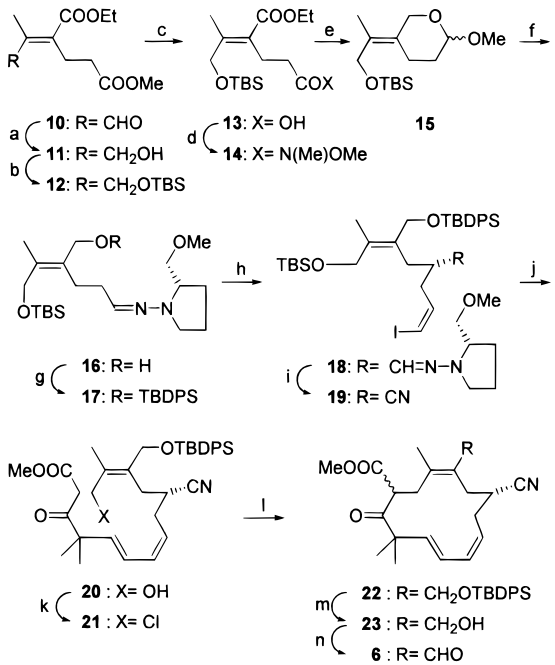
(+)-Maritimol (**1**), a member of the stemodane diterpenoids (**1**−**3**), was isolated[1] from *Stemodia maritima* L. (Scrophulariaceae) and used as a Caribbean folk medicine for treatment of venereal diseases. It represents a long-standing synthetic challenge[2] with its unique tetracyclic stemodane framework and the construction of its seven chiral centers, particularly the two central, adjacent quaternary carbons at positions 9 and 10. Reported in this contribution is the first asymmetric total synthesis of (+)-maritimol, applying the TADA strategy, developed in our laboratory (Scheme 1).[3a]

Scheme 1



From a synthetic point of view, the A.B.C[6.6.5] *trans*−*syn*−*cis* (TSC) ring system of maritimol correlated well[4a] with our previous fundamental TADA model studies, having demonstrated the stereospecific transformation of 14- and 15-membered *trans*−*cis*−*cis* (TCC) macrocyclic trienes to the respective A.B.C[6.6.6][4b] and [6.6.7][4c] TSC-tricycles. It was also shown that even tetrasubstituted dienophiles were tolerated, particularly when they were activated.[4a,c] Moreover, a discovery that a stereogenic center on the macrocycle at the maritimol *pro*-12 position may induce perfect diastereoface selection in the TADA reaction was also made.[4a]

Scheme 2[a]



[a] Reagents: (a) $NaBH_4$, MeOH, >73%. (b) Imidazole, TBS−Cl, 95%. (c) NaOH, THF, 5 °C, 96%. (d) Carbonyldiimidazole then Et_3N and NH(OMe)Me·HCl, 89%. (e) DIBALH, CH_2Cl_2, −78 °C then MeOH, 89%. (f) SAMP, PTSA (cat.), PhH, 80 °C, 93%. (g) Imidazole, TBDPS−Cl, 100%. (h) LDA, 0 °C then **8**, THF, −100 °C, 83%. (i) Mg-monoperoxyphthalate, MeOH/Et_2O, 98%. (j) Py·HF, THF then **9**, $PdCl_2$·$(MeCN)_2$, DMF, 52%. (k) $(Cl_3C)_2CO$, PPh_3, CH_2Cl_2, −78 to 0 °C, 94%. (l) Cs_2CO_3, CsI, MeCN, 80 °C, 75%. (m) TBAF, THF, 87%. (n) Dess−Martin periodinane, 91%.

Retrosynthetic analysis suggests that tetracycle **4**, a central advanced intermediate of stemodanes,[2a] is available via TSC-tricycle **5** corresponding[4] to macrocycle **6** (Scheme 1). This chiral macrocycle, in turn, can be made in a highly convergent manner, starting from tetrasubstituted *cis*-dienophile **7**. Following an introduction of the requisite asymmetry via (*S*)-*N*-amino-2-(methoxymethyl)pyrrolidine (SAMP)[5] hydrazone-based alkylation with *Z*-1,3-diiodo-propene (**8**),[6] a Stille coupling[7] with stannane **9**[8] delivers the ω-functionalized acyclic β-ketoester substrate for macrocyclization.

The actual synthesis began with aldehyde **10** (Scheme 2), available in two steps (70%) from commercial Hagemann's ester.[9] $NaBH_4$ reduction and silyl protection provided tetrasubstituted *cis*-dienophile **12** (70%), which was selectively hydrolyzed to monoacid **13** (93%) and further transformed into Weinreb amide **14** (89%).[10] Parallel reduction (DIBAL-H) of both carbonyls afforded, after a methanol quench, methoxytetrahydropyran **15**, which could be easily transformed to SAMP[5] hydrazone **16** (83%).

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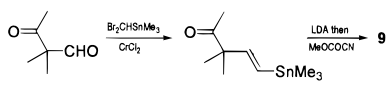
(8) Prepared in two steps in 67% overall yield according to: (a) Cliff, M. D.; Pyne, S. G. *Tetrahedron Lett.* **1995**, *36*, 763−766. (b) Crabtree, S. R.; Mander, L. N.; Sethi, S. P. *Org. Synth.* **1991**, *70*, 256−264.



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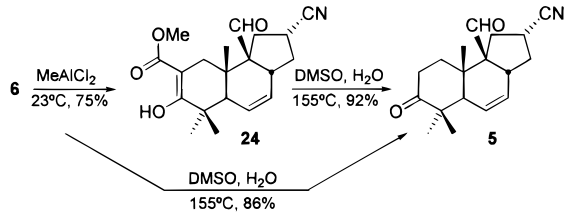
Scheme 3

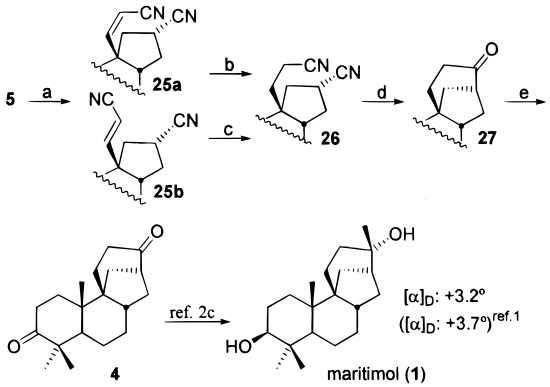


Silylation followed by alkylation[5] of **17** with iodide **8**[6] gave chiral vinyl iodide **18** (83%, >90% de). Oxidation[11] of **18** afforded the corresponding nitrile **19**. Selective deprotection and Stille coupling[7] with stannane **9**[8] delivered acyclic triene **20** in 68% yield. Chlorination[12] produced ω-chloro-β-ketoester **21** (94%) which, upon macrocyclization[4] with Cs_2CO_3 under high dilution, gave 13-membered TCC macrocycle **22** (75%).[13] Desilylation to alcohol **23** (87%) and oxidation[14] provided macrocyclic aldehyde **6** (91%).

Treatment of a dichloromethane solution of **6** (Scheme 3) with $MeAlCl_2$ for 7 h at 23 °C, provided exclusively TSC tricycle **24** (75%)[15] in its completely enolized form. Thermal demethoxycarbonylation[16] of **24** for 3 h gave tricycle **5**. Moreover, heating **6** under the same conditions for 4 h gave directly tricycle **5** (87%) offering an efficient procedure for large-scale preparations.[17] It is remarkable that both Lewis acid catalyzed and thermic TADA reactions exhibit similar complete stereoface- and diastereospecificity induced by a small remote nitrile group. This observation is in total accord with our previous model studies.[4a]

Construction of ring D of the stemodane skeleton was started with a Peterson olefination[18] affording a 6:1 isomeric mixture of *cis*- and *trans*-enenitrile **25a** and **25b**, respectively, (79%) (Scheme 4). Due to an easy separation of these isomers with flash column chromatography, the subsequent reductions could be optimized individually. Accordingly, while **25a** could be reduced by catalytic hydrogenation without difficulty, the higher pressure, necessary to reduce the *trans*-olefin, was not compatible with **25b**. However,

Scheme 4[a]



[a] Reagents and conditions: (a) TMS−CH(CN)B(O^iPr)$_2$, THF, −78 °C, 79% (84% corr.). (b) H_2/Pd/C, EtOAc, AcOH, 1 bar, 87%. (c) Mg, MeOH, 0 °C, 64%. (d) KO^{t}Bu, ^{t}BuOH, 85 °C then AcOH/H_3PO_4, 115 °C, 68%. (e) H_2/Pt/C, EtOAc, 40 bar then Dess−Martin periodinane, CH_2Cl_2, 84%.

this reduction could be achieved via a magnesium−methanol system[19] in a moderate 64% yield to converge the sequence in dinitrile **26**. Conclusion of the synthesis was developed from Piers' racemic synthesis.[2c] A Thorpe−Ziegler annulation of **26** and an acidic hydrolysis of the intermediate enaminonitrile provided tetracycle **27** (68%). Catalytic hydrogenation and a subsequent oxidative adjustment[14] delivered dione **4** (85%).[20] Since (±)-**4** has long been established as a central advanced intermediate in the syntheses of stemodane diterpenoids (±)-**1**, (±)-**2**, and (±)-**3**,[2a] our synthesis constitutes a formal asymmetric total synthesis of these stemodanes. Accordingly,[2c] our representative target **1** could be acquired in two further steps from **4**.[21]

In summary, a highly convergent 22-step asymmetric synthesis of (+)-maritimol has been achieved from easily available aldehyde **10**. At the heart of the synthesis is a TADA reaction of an appropriately functionalized, 13-membered TCC macrocycle with a tetrasubstituted, activated dienophile prepared in only 15 steps. This strategic step displays a complete stereoface- and diastereospecificity to generate four new stereogenic centers induced by a remote nitrile appendage. A detailed account will follow in due course.

Acknowledgment. We are grateful to Professor Charles D. Hufford of University of Mississippi for an authentic sample of (+)-maritimol. A Basic Research Chair in organic chemistry granted to Pierre Deslongchamps by BioChem Pharma and a financial support from NSERC-Canada are highly appreciated.

Supporting Information Available: Experimental procedures and listing of spectral data (IR, MS, ^{1}H and ^{13}C NMR) for all synthetic compounds, and ^{1}H and ^{13}C NMR spectra of natural and synthetic **1** (PDF). This material is available free of charge via the Internet at http//pubs.acs.org.

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(13) Easily separable O-alkylated macrocycle (3%) was also formed as a single isomer.

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(15) When demethoxycarbonylated **6** was subjected to TADA reaction, Lewis acid treatment or heating caused intensive decomposition. A detailed investigation of the TADA reaction including the origin of its stereoface- and diastereospecificity will be the subject of another article.

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(17) It was also demonstrated, with parallel oxidations of separated epimers of **23**, and subsequent Lewis acid catalyzed or thermic TADA reactions that the epimers of **6** would converge into tricycles **24** or **5**, respectively, with comparable yields. In large-scale preparations, an epimeric mixture of **6** was used.

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(20) An unusually large catalyst load and high pressure is required to hydrogenate the extra double bond in ring B. Although these extreme conditions had prevented an earlier parallel hydrogenation of diene **25**, here an inevitable overreduction was not terminal.

(21) Synthetic (+)-maritimol is identical in all respects (^{1}H and ^{13}C NMR, IR, TLC) with a natural sample.