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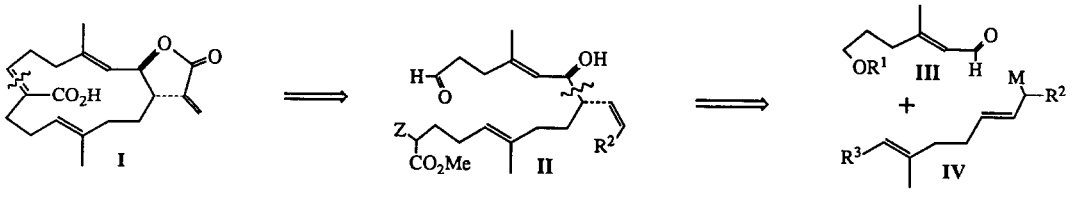
STEREOSELECTIVE TOTAL SYNTHESIS OF THE CEMBRANOLIDE DITERPENE ANISOMELIC ACID

James A. Marshall* and Bradley S. DeHoff
Department of Chemistry, University of South Carolina
Columbia, South Carolina 29208

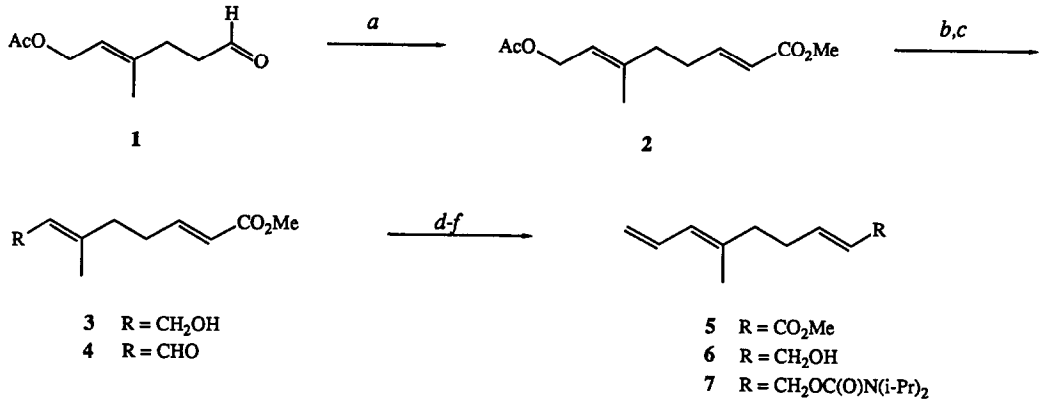
Abstract: A highly stereoselective total synthesis of the cembranolide diterpene anisomelic acid has been achieved via a convergent route. Macrocyclization was effected by a (Z)-selective intramolecular Horner-Emmons condensation.

Cembranolides, 14-membered diterpene lactones, are a widespread class of natural products with interesting structural and biological properties.[1] Although interest in the synthesis of cembranes has increased dramatically in recent years,[2] to date only one total synthesis of a natural cembranolide diterpene has been reported.[3] Herein we detail the total synthesis of (±)-anisomelic acid (I), a cembranolide constituent of the South Indian medicinal plant *Anisomeles malabarica* R. Br.[4]



Our synthetic plan, outlined above, envisioned anti-selective[5] coupling of an allylmetal derivative IV with a conjugated aldehyde III to establish the eventual lactone stereochemistry.[6] The method of Hoppe employing metallated allyl carbamates seemed especially well suited to our purposes as it promised high anti selectivity and it produced an enol carbamate whose further elaboration to the requisite acetic acid side chain appeared readily feasible.[7] Macrocyclization would be achieved via an intramolecular Horner-Emmons condensation. The stereoselectivity of this step was of considerable interest in view of the moderate selectivities recently reported for applications of a similar nature.[8]

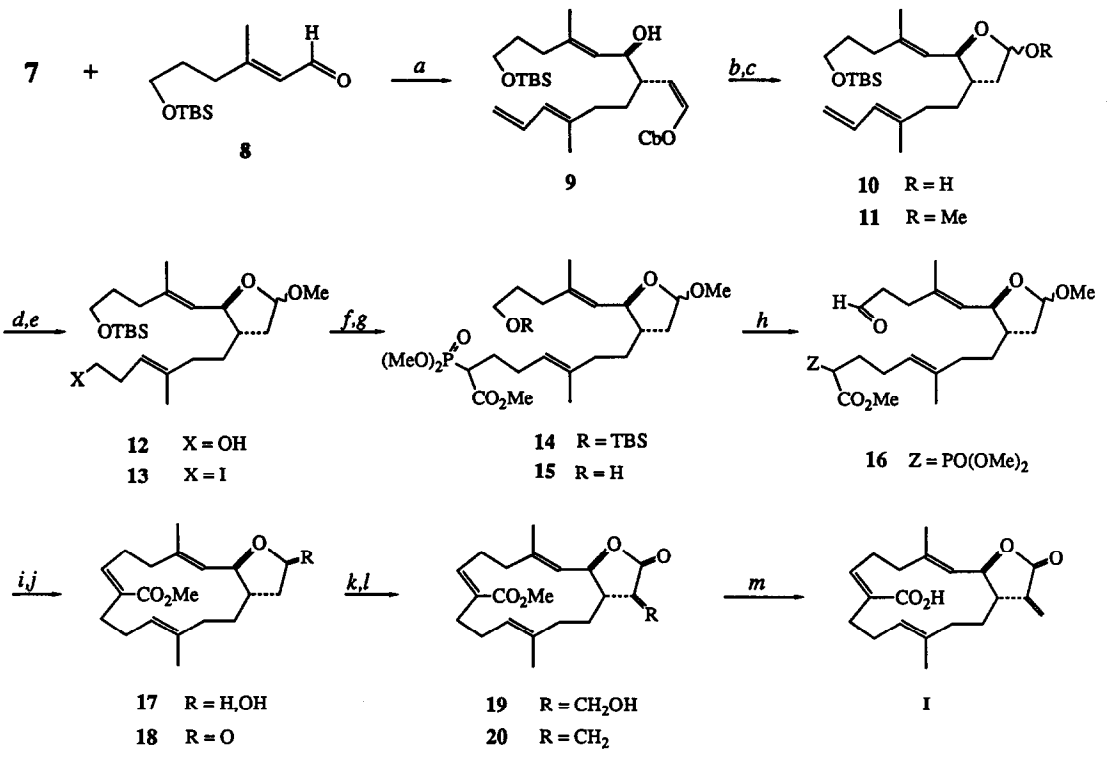
Aldehyde 1, the starting material for both halves (III and IV) of our coupling scheme, was readily available through ozonolysis of geranyl acetate.[9] Condensation with methyl α-triphenylphosphorylideneacetate afforded the trans conjugated ester 2 with high stereoselectivity.[10] Methanolysis of the acetate followed by Swern oxidation[11] yielded the aldehyde ester 4. Attempted Wittig methylenation of this aldehyde proceeded poorly so two-step Peterson olefination was employed to produce trienoate 5.[12] Treatment of the derived alcohol with *N,N*-diisopropylcarbamoyl chloride gave the desired carbamate 7.



a) $Ph_3P=CHCO_2Me$, CH_2Cl_2, -20°C, 86%, 99:1 trans:cis; b) K_2CO_3, MeOH, 0°C; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C, 80%, 2 steps; d) $TMSCH_2MgCl$, THF; AcCl, -10°C, 82%; e) DIBAH, CH_2Cl_2-hexanes, -78°C; f) $(i\text{-}Pr)_2NCOCl$, NaH, DME, 89%, 2 steps

Lithiation of carbamate **7** followed by addition of triisopropoxy chloro titanium (IV)[6] and then aldehyde **8**[13] gave rise to the homoallylic alcohol **9** with virtually complete diastereoselectivity.[14] In view of the expected acid lability of the allylic alcohol and silyl ether functions of **9** we did not pursue acid hydrolysis of the enol carbamate.[7] Instead, cleavage was effected with lithium aluminum hydride leading to lactol triene **10**. The lactol methyl ether derivative **11** underwent selective hydroboration at the terminal double bond giving alcohol **12**. The derived homoallylic iodide **13** afforded the phosphono ester **14** in high yield via displacement with sodio trimethyl phosphonoacetate in DMSO at room temperature. Cleavage of the TBS ether followed by Swern oxidation[11] led to the cyclization substrate, phosphono ester aldehyde **16**.

Initial cyclization studies were conducted with the trifluoroethyl phosphonate **16**, Z=PO-$(OCH_2CF_3)_2$, in order to maximize production of the (*Z*)-product **17** (R=H, OMe).[15] Neither KHMDS nor KO-*t*-Bu in THF-18-crown-6 gave cyclic product; at low temperature (-78°C) starting material was recovered and at higher temperature (-78° to 0°C) decomposition occurred. However, K_2CO_3 in toluene-18-crown-6 afforded the (*Z*) cyclic ester **17** as the sole detectable isomer in 34% yield.[14] Cyclization of the methyl phosphonate **16** proved equally effective. Best results were obtained with NaH in DME, 18-crown-6 followed by *in situ* hydrolysis and oxidation to give the crystalline lactone ester **18** in 40% overall yield. The structure of this key intermediate was ascertained through high field ^1H NMR and single crystal X-ray structure analysis.[16]



a) *n*-BuLi, ether, TMEDA, ClTi(O-*i*-Pr)$_3$, -78° to -10°C, 60-78%; b) $LiAlH_4$, THF, reflux, 84%; c) $HC(OMe)_3$, ppts, CH_2Cl_2; d) $(Siam)_2BH$; H_2O_2, NaOH, 82%, 2 steps; e) Ph_3P, I_2, imidazole, 3:1 THF-CH_3CN, -10°C, 80-90%; f) $(MeO)_2POCH_2CO_2Me$, NaH, DMSO, 85%; g) ppts, MeOH, reflux; h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C, 87%, 2 steps; i) NaH, DME, 18-crown-6; 10% HCl; j) PCC, NaOAc, Celite, CH_2Cl_2, 40%, 3 steps; k) LDA, CH_2O gas generated in a stream of argon, 75% based on consumed starting material; l) 1-cyclohexyl-3-(2-*N*-methylmorpholinoethyl)carbodiimide p-toluenesulfonate, CH_3CN, cat. $CuCl_2$, 60°C; m) KOH, 2:1 H_2O-EtOH, reflux; H_2O, HCl, 84%

Hydroxymethylation of lactone 18 was effected by treatment with 1.0 equiv of LDA in THF at -78°C followed by addition of gaseous formaldehyde. Careful control of experimental conditions was required as excess base caused deconjugation of the ester double bond and gave rise to a complex mixture. The crude hydroxymethylated lactone 19 was dehydrated with *N*-cyclohexyl,*N*-2-(N-methylmorpholino)ethylcarbodiimide *p*-toluenesulfonate[17] to yield the methylene lactone 20. Saponification and subsequent acidification of the (presumed) diacid salt afforded (±)-anisomelic acid I. Identity with natural material was established by comparison of TLC mobility and high field ^1H NMR spectra.

Acknowledgement. We are indebted to Dr. K. K. Purushothaman, Assistant Director-in-Charge, Captain Srinivasa Murti Drug Research Institute for Ayurveda, for an authentic sample of anisomelic acid. Support from the National Institute of General Medical Sciences through research grant 5-RO1 GM29475 is gratefully acknowledged. We thank the NSF for funding of an AM-300 NMR spectrometer through instrument grant CHE-8411172.

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13. Aldehyde **8** could be prepared from **1** by the sequence (i) $NaBH_4$; EtOH; (ii) TBSCl, DMAP, Et_3N; (iii) K_2CO_3, MeOH; (iv) Swern oxidation.[11] For an alternative route, see Marshall, J. A.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 863.

14. The conditions for macrocyclization were patterned after those first reported for β-keto phosphonates by P. A. Aristoff (*J. Org. Chem.* **1981**, *46*, 1953) and later used in macrolide synthesis by K. C. Nicolaou, S. P. Sietz and M. R. Pavia (*J. Am. Chem. Soc.* **1982**, *104*, 2030). Ester phosphonates such as **16** are less acidic and appear to cyclize less readily than their ketophosphonate counterparts.

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16. We are indebted to Dr. Lukasz Lebioda, Department of Chemistry, University of South Carolina for this analysis.

17. The reagent is available from Aldrich Chemical, Milwaukee, WI. Its application to lactone methylenation was developed by R. C. Andrews of our laboratory.

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