Pergamon

Tetrahedron Letters, Vol. 38, No. 8, pp. 1271-1274, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00069-5

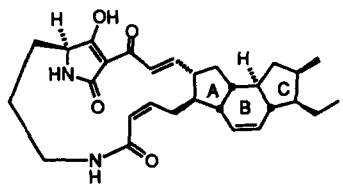
SYNTHETIC STUDIES ON SPINOSYN A. CONVENIENT ENANTIOSELECTIVE CONSTRUCTION OF A SUITABLY FUNCTIONALIZED *trans,anti,cis*-DECAHYDRO-*as*-INDACENE INTERMEDIATE VIA [3.3] SIGMATROPY AND DOUBLE CONFIGURATIONAL INVERSION

Leo A. Paquette,* Zhongli Gao, Zhijie Ni, and Graham F. Smith

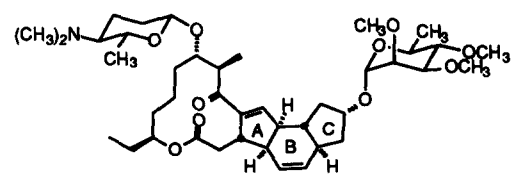
Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

Abstract: An enantioselective route to the decahydro-*as*-indacene **15** is described. Anionic oxy-Cope rearrangement of alcohol **5** initiates the sequence, which capitalizes on thermodynamics to control ultimate elaboration of the four key stereogenic centers resident in the several intermediates.

Recently, there has been discovered a growing collection of biologically active microbiological products that possess a perhydro-*as*-indacene subunit in their framework. Two of the more prominent members are the antibiotic ikarugamycin (**1**)[1,2] and the insecticide spinosyn A (**2**).[3,4] Of more than passing interest is the antipodal relationship between the tricyclic cores of natural **1** and **2**. All of the constructive approaches to date[2a,e,4,5] except for those developed in this laboratory[2b-d] and by Whitesell[6] have involved an intramolecular Diels-Alder reaction as the principal strategy tactic. Our total synthesis of (+)-**1** defined a practical means for generating such ring systems by means of anionic sigmatropy. Herein the feasibility of applying oxy-Cope technology to the spinosyn A problem is demonstrated, with particular focus on suitable control of the thermodynamic preferences resident in these polycyclic networks.[2c,7]



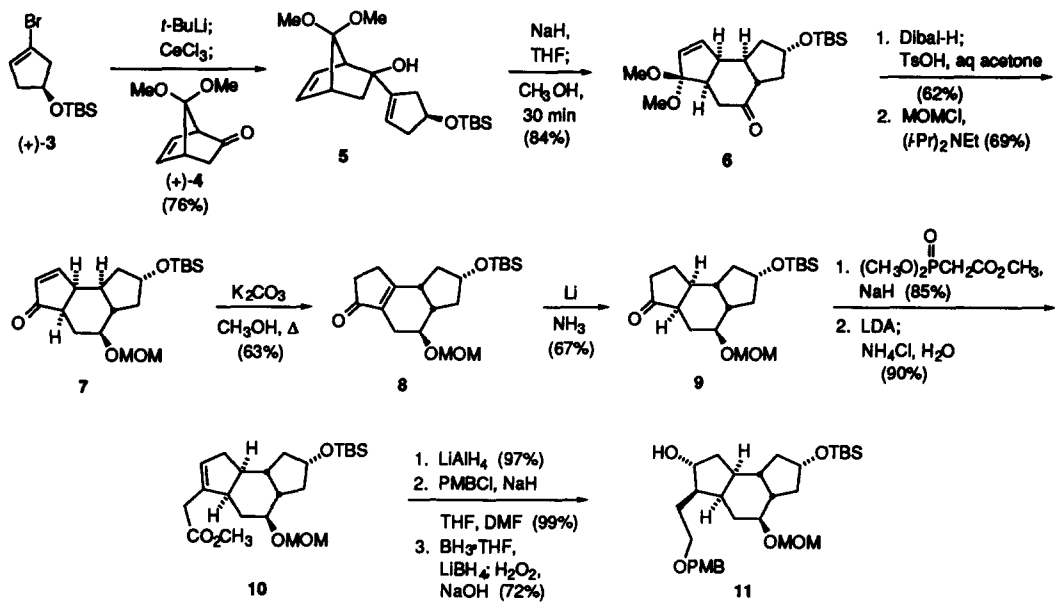
(+)-**1**



(-)-**2**

The point of departure consisted of cerium trichloride-mediated coupling[8] of lithiated (*S*)-**3**, readily available from (4*R*)-*tert*-butyldimethylsiloxy-2-cyclopenten-1-one,[9] to (+)-**4**[10] (Scheme 1). Sigmatropic rearrangement within the resulting exo alcohol **5** via a boat-like transition state is

Scheme 1

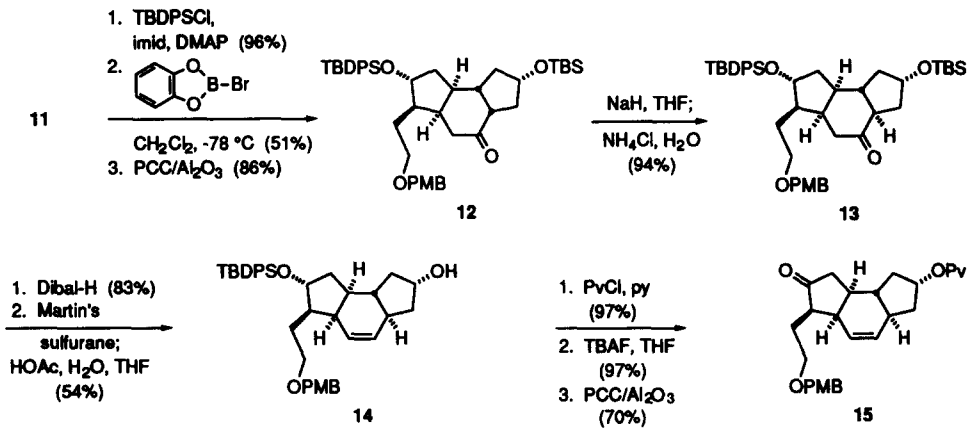


sufficiently rapid that sodium can be used as the counter ion in the absence of a crown ether. Following a methanol quench, epimerization is complete within 30 min and only ketone **6** is obtained. It is imperative to recognize that the absolute configuration of *both* stereogenic centers at the conjoined B/C rings have been *purposely inverted* in order to accommodate the ensuing chemistry.

Stereocontrolled reduction of the carbonyl functionality, acetal hydrolysis, and MOM protection resulted in conversion to **7**, thereby setting the stage for base-promoted internalization of the cyclopentenone double bond. Relevantly, this isomerization proceeds with total configurational inversion at the tertiary allylic site. The contrasting thermodynamic preferences at play within **6** and **8** are noteworthy. When **8** was subjected to dissolving metal reduction, the *cis,anti,cis* ketone **9** was generated in keeping with the stereochemical control elements normally associated with this process. Three of the four perhydro-*as*-indacene stereocenters had now been properly set.

Further advance toward **2** was achieved by subjecting **9** to the Wadsworth-Emmons reaction. Migration of the double bond to the β,γ-position within the five-membered ring without loss of the cis-A/B arrangement was efficiently achieved (90%) by kinetic deprotonation followed by quenching with aqueous ammonium chloride solution. Arrival at **10** in this manner allowed for conversion to **11** by way of a conventional hydroboration sequence.

Scheme 2



In order to effect introduction of the double bond in ring B while simultaneously enabling ultimate macrolactone assembly, **11** was silylated, the MOM group was selectively removed by means of bromocatecholborane,[11] and oxidation to ketone **12** was undertaken (Scheme 2). It was well appreciated[2c] at this point that **12** should be amenable to epimerization. Indeed, its conversion to **13** in essentially quantitative yield could be readily accomplished. Ketone **13** was reduced with Dibal-H and dehydrated with the Martin sulfurane reagent.[12] When the workup protocol involved hydrolysis with aqueous acetic acid in THF, the *tert*-butyldimethylsilyl functionality that had served us so well from the outset was selectively removed. Following the acquisition of **14**, pivaloylation and generation of a carbonyl group in ring A gave rise to **15**.[13]

Thus, we have developed the thermodynamic stabilities associated with various perhydro-*as*-indacenes in combination with the powerful scaffolding capability of the oxy-Cope rearrangement into an effective means for constructing the non-macrolide sector of the spinosyns. Advantage was taken of the fact that the pair of cyclopentanes prefer to be fused anti across the "rear" sector of the central cyclohexane ring, and that an overall cis,anti,trans arrangement is more stable than the cis,anti,cis option. We hope to report on the elaboration of **2** from **15** in due course.

Acknowledgments. The funding for this research was generously provided by the National Institutes of Health. Z.N. was an Ohio State University Postdoctoral Fellow, 1989-1990.

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(3) Isolation: Kirst, H. A., et al., ACS Symposium Series 504; American Chemical Society: Washington, DC, 1992; pp 214-225, and references cited therein. The names initially adopted for **2** (LY232105, A83543A, and lepicidin A) have been recently abandoned in favor of spinosyn A (Kirst, A.; communication dated June 7, 1994).

(4) Synthesis: Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 2260; **1993**, *115*, 4497.

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(10) The resolution of racemic **4** was accomplished by means of Johnson's sulfoximine procotol [Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021].

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(*Received in USA* 13 *December* 1996; *accepted* 2 *January* 1997)