Asymmetric Total Synthesis of (–)-Secodaphniphylline[1]

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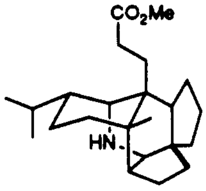
Summary: An asymmetric total synthesis of (–)-secodaphniphylline (**5**) is described. The desired absolute stereochemistry is established in two stereoselective transformations—an asymmetric Michael reaction of amide **8** and an asymmetric reduction of ketone **14**.

The *Daphniphyllum* alkaloids are a family of squalene-derived natural products having diverse and complex structures.[2] Most members of the group have truncated structures, in which only 22 skeletal carbons of the biogenetic progeniter remain. Examples are methyl homosecodaphniphyllate (**1**), methyl homodaphniphyllate (**2**), daphnilactone A (**3**),[3] and yuzurimine (**4**). In the known *Daphniphyllum* alkaloids that retain the entire complement of squalene carbons the first eight carbons of squalene molecule are fashioned into a bicyclic array, as exemplified in the structures of the C_{30} *Daphniphyllum* alkaloids secodaphniphylline (**5**) and daphniphylline (**6**). We have reported total syntheses of racemic versions of alkaloids **1**–**3**.[1,4] However, apart from a synthesis of (±)-*proto*-daphniphylline (**7**), the conjectured biosynthetic pentacyclic parent of the entire family,[5] none of the C_{30} *Daphniphyllum* alkaloids have been fabricated.

In this paper we report a total synthesis of (–)-secodaphniphylline (**5**). The convergent route employed uses an asymmetric Michael addition to acquire an enantiomeric excess in the pentacyclic nitrogen-containing moiety and an asymmetric carbonyl reduction for the same purpose in preparation of the 2,8-dioxabicyclo[3.2.1]octane unit. The enantiomeric purity available in the two synthetic subunits (90–92% ee) is greatly magnified in the coupling reaction, and the synthetic (–)-secodaphniphylline is calculated to be approximately 99.6% ee.

The synthesis of (–)-**1** is summarized in Scheme I. Amide **8** was prepared from 5-(benzyloxy)pentanoyl chloride and (*S*,*S*)-2,5-dimethylpyrrolidine[6] under Schotten–Baumann conditions. A tetrahydrofuran (THF) solution of the lithium enolate of **8** was treated with unsaturated ester **9** and then with a solution of homogeranyl iodide in hexamethylphosphoric amide (HMPA) at –78 °C. The major product, homogeneous under several chromatographic conditions, was isolated in 64% yield. For reasons to be explained shortly, we believe that this product is actually a mixture of two diastereomers in a ratio of approximately 92:8, with the major isomer being **10** and the minor one being enantiomeric at each of the three stereocenters created in the Michael and alkylation reactions. The Michael addition, then, occurs with an enantioselectivity of 84% ee, in accord with expectations on the basis of a similar reaction reported by Yamaguchi.[7] Reduction of **10** proceeded without incident, providing hydroxy amide **11** (73%), which was converted into lactone **12** by treatment with 5 N KOH in ethylene glycol at 165 °C for 50 h, followed by acidification (92%). The conversion of scalemic[8] **12** into (–)-methyl homosecodaphniphyllate (**1**) exactly parallelled the previously reported synthesis of the racemic alkaloid.[3b] The material so obtained had mp 77–80 °C and $[\alpha]_D = -82°$ ($c = 1.12$, $CHCl_3$), corresponding to 83% ee. Recrystallization from hexane gave material with mp 98–99 °C and $[\alpha]_D = -88°$ ($c = 0.31$, $CHCl_3$), corresponding to 90% ee.[9]



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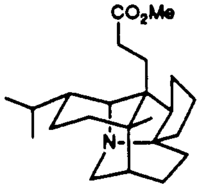

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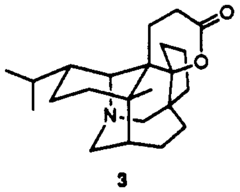

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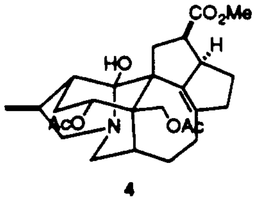

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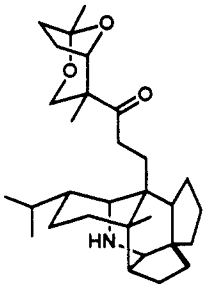

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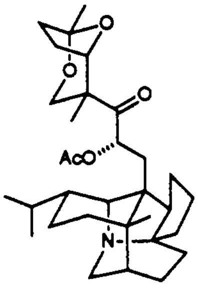

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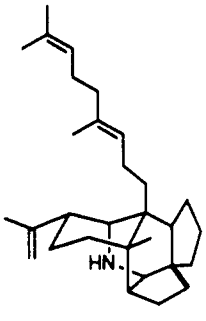

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The characteristic *Daphniphyllum* 2,8-dioxabicyclo-[3.2.1]octane unit was prepared starting with ketal acid **13**[10] as shown in Scheme II. Treatment of the derived *N*-methoxy-*N*-methylamide [(1) carbonyldiimidazole, CH_2Cl_2, 10 min; (2) *N*,*O*-dimethylhydroxylamine hydrochloride][11] with 1-butynyllithium in THF gave ketone **14** (86%). Compound **14** was reduced with the $LiAlH_4$/Darvon alcohol complex[12] at –80 °C in ether to obtain

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[1] Part 8 in a series of papers on the *Daphniphyllum* alkaloids. For part 7, see: Ruggeri, R.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3714.

[2] (a) Yamamura, S.; Hirata, Y. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic: New York, 1975; Vol. 15, p 41. (b) Yamamura, S.; Hirata, Y. *Int. Rev. Sci., Org. Chem., Ser. 2* **1976**, *9*, 161. (c) Yamamura, S. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1986; Vol. 29, p 265.

[3] Daphnilactone A actually has 23 carbons, the additional one presumably arising from a formaldehyde equivalent: (a) Yamamura, S.; Terada, Y. *Chem. Lett.* **1976**, 1381. (b) Ruggeri, R. B.; Heathcock, C. H. *Pure Appl. Chem.* **1989**, *61*, 289.

[4] (a) Heathcock, C. H.; Davidsen, S. K.; Mills, S.; Sanner, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 5650. (b) Ruggeri, R. B.; Hansen, M. M.; Heathcock, C. H. *Ibid.* **1988**, *110*, 8734. (c) Ruggeri, R. B.; McClure, K. F.; Heathcock, C. H. *Ibid.* **1989**, *111*, 1530.

[5] Piettre, S.; Heathcock, S. *Science (Washington, D.C.)* **1990**, *248*, 1532.

[6] (a) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1977**, *42*, 1663. (b) Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083.

[7] Yamaguchi, M.; Hasabe, K.; Tanaka, S.; Minami, T. *Tetrahedron Lett.* **1986**, *27*, 959.

[8] The term scalemic has been suggested by James Brewster (Purdue University) to describe an unequal mixture of enantiomers. According to Brewster's suggestion, scalemic and racemic are macroscopic analogues of chiral and achiral, adjectives that should be reserved for single objects such as molecules.

[9] Natural (–)-methyl homosecodaphniphyllate has mp 102.5–3 °C (ref 16). Although the optical rotation is not reported in the literature, we have found $[\alpha]_D = -97°$ ($c = 0.79$, $CHCl_3$) with a sample provided by Prof. Yamamura.

[10] Bruice, T. C.; Piszkiewicz, D. *J. Am. Chem. Soc.* **1967**, *89*, 3568.

[11] Nahm, S.; Weinreb, S. *Tetrahedron Lett.* **1981**, *22*, 3815.

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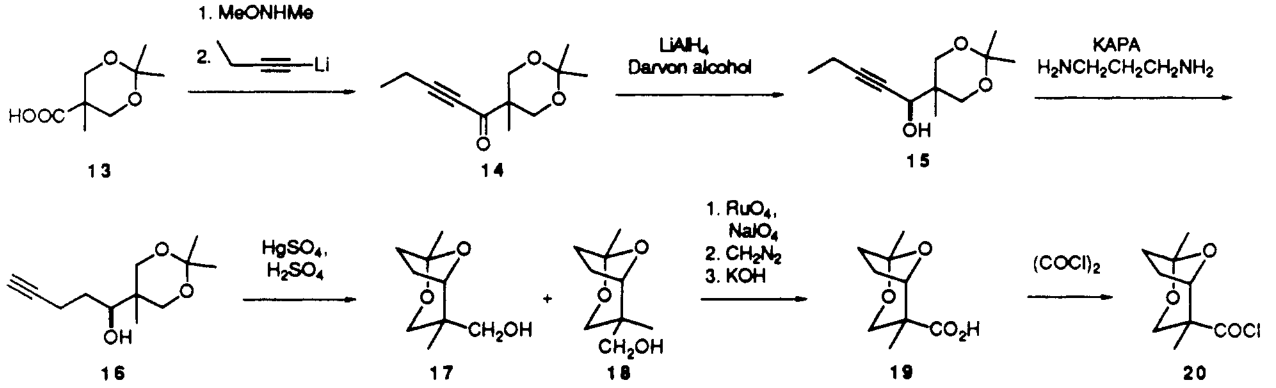
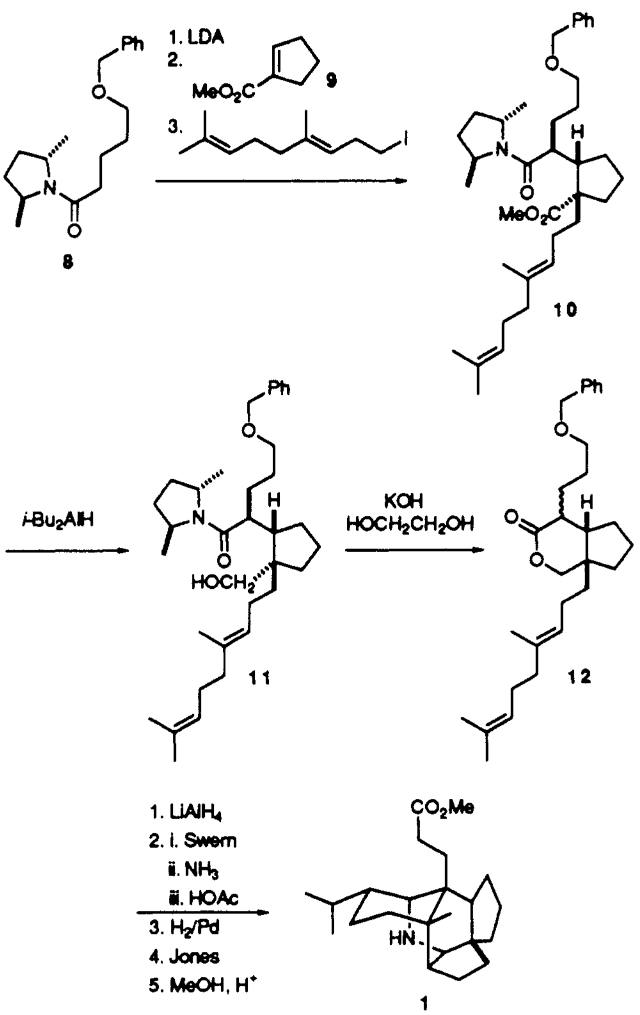
Scheme I



Scheme II



alcohol **15** (93%), shown by conversion into the ester of (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid[13] to be 92% ee. Treatment of (−)-**15** with potassium 3-aminopropanamide (KAPA)[14] in 1,3-propanediamine at −15 °C for 45 min afforded alcohol **16** (87%). Treatment of **16** with mercuric sulfate and dilute sulfuric acid in THF provided bicyclic hydroxy ketals **17** and **18** as a 5:1 mixture in 95% yield.[15] Oxidation of the **17**/**18** mixture with ruthenium tetroxide and sodium periodate[16] gave the corresponding mixture of acids, which were esterified with diazomethane. The resulting esters are easily separated by chromatography on silica gel. The major isomer was saponified with alcoholic KOH to provide ketal acid **19**, mp 105–7 °C, in 31% yield, based on the mixture of hydroxy ketals. The enantiomeric purity of **19** was found to be 92% ee by application of Mosher's method[13] to the corresponding primary alcohol. Treatment of **19** with oxalyl chloride furnished acyl chloride **20** (100%).

Mixed Claisen coupling was accomplished by treating the lithium enolate of (−)-**1** in THF with **20** in THF at −78 °C. The resulting mixture of diastereomeric β-keto esters was treated with sodium cyanide in dimethyl sulfoxide at 150 °C to produce in 43% yield (−)-secodaphniphylline, mp 124–5 °C, $[\alpha]_D = -50 \pm 1°$ (c = 0.35, $CHCl_3$) (lit.[17] mp 129–30 °C, $[\alpha]_D = -51 \pm 0.5°$ (c = 1.06, $CHCl_3$)).[18,19] The calculated enantiomeric purity of the synthetic secodaphniphylline is 99.6%.[20,21]

Acknowledgment. This work was supported by a grant from the National Science Foundation (CHE-84-18437) and by fellowships granted to J.A.S. by Smith, Kline, and French Research Laboratories and the United States Public Health Service. We thank Professor S. Yamamura for a sample of natural secodaphniphylline.

Supplementary Material Available: Spectral data for all of the new compounds and intermediates reported; IR and 500-MHz ^1H NMR spectra of synthetic and natural secodaphniphylline; expansion of the δ 2.4–4.8 region in the 500-MHz ^1H NMR spectra of synthetic secodaphniphylline and a 2:1 mixture of the racemic alkaloid and its diastereomer (12 pages). Ordering information is given on any current masthead page.

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[12] (a) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870. (b) Cohen, N.; Lopresti, R. J.; Neukom, C.; Saucy, G. *Ibid.* **1980**, *45*, 582.

[13] Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

[14] (a) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891. (b) Midland, M. M.; Halterman, R. L.; Brown, C. A.; Yamaichi, A. *Tetrahedron Lett.* **1981**, *22*, 4171.

[15] The racemic counterparts of **17** and **18** have been prepared previously: Irikawa, H.; Ishikura, T.; Okumura, Y. *Bull. Chem. Soc., Jpn.* **1977**, *50*, 2811.

[16] Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

[17] Toda, M.; Hirata, Y.; Yamamura, S. *Tetrahedron Lett.* **1972**, *28*, 1477. We observed mp 119–121 °C (sealed capillary) for an authentic sample of (−)-**5** provided by Prof. Yamamura.

[18] The uncertainty in $[\alpha]$ is due to the uncertainty in weighing precision.

[19] Similar coupling of (±)-**1** and (±)-**20** gave in 44% yield a 2:1 mixture of (±)-secodaphniphylline and the diastereomer resulting from coupling of the major enantiomer of **1** with the minor enantiomer of **20** (and vice versa).

[20] The calculation is based on the enantiomeric purities of the **1** and **20** (95:5 and 96:4, respectively). It has been pointed out previously that coupling of two enantiomerically enriched units can lead to a major diastereomer of much higher enantiomeric purity than either reactant. (a) Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 576. (b) Midland, M. M.; Gabriel, J. *Ibid.* **1985**, *50*, 1144.

[21] Although the calculated ratio of (−)-**5** and its diastereomer is 96:4, we are unable to detect the diastereomer in the 500-MHz ^1H NMR spectrum of the reaction product (see the supplementary material for an expansion of a diagnostic region of the spectrum of synthetic (−)-**5**).