The practicability of this new method is one of its more attractive aspects: (1) chiral sources (tartaric acids) are easily obtainable in both enantiomeric forms at low cost, and thus either of the enantiomers can be synthesized with high enantiomeric excess (Scheme I); (2) simple α,β-unsaturated aldehydes can be used without any derivatizations, making further transformation of the adduct easy; (3) only a catalytic amount (10 mol % or less) of chiral Lewis acid is needed; (4) the operation is simple without any complexity in the workup or isolation procedure so that excellent reproducibility is available.

The present enantioselective, catalytic C–C bond forming process is discriminating to a degree barely rivaled by any other stoichiometric process. Further application of the CAB catalyst as chiral Lewis acid to other reactions is now under investigation.

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Kyoji Furuta, Sadahiro Shimizu
Yoshikazu Miwa, Hisashi Yamamoto*
Department of Applied Chemistry
Nagoya University
Nagoya 464-01, Japan
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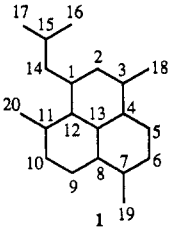
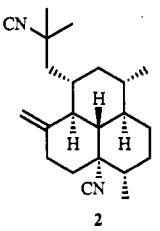
Total Synthesis of (±)-8,15-Diisocyano-11(20)-amphilectene

Summary: With 2-(methoxycarbonyl)-3-methylcyclohexanone and (*E*)-1-(*tert*-butyldimethylsiloxy)-6-iodo-3-(trimethylstannyl)-2-hexene as starting materials, the structurally novel, antimicrobial diterpenoid (±)-8,15-diisocyano-11(20)-amphilectene (**2**) was synthesized in 20 steps.

Sir: The structurally novel and biologically interesting amphilectane family of diterpenoids, which possess the basic carbon skeleton **1**, have been isolated from marine sponges.[1-3] One member of this group of natural products, (−)-8,15-diisocyano-11(20)-amphilectene, was obtained from *Hymeniacidon amphilecta* and was shown by X-ray diffraction analysis to possess the constitution and relative stereochemistry shown in **2**.[1] We report here a stereocontrolled synthesis of (±)-**2**.



1



2

Alkylation (PhMe, reflux, 48 h) of the potassium enolate of 2-(methoxycarbonyl)-3-methylcyclohexanone[4] with (*E*)-1-(*tert*-butyldimethylsiloxy)-6-iodo-3-(trimethylstannyl)-2-hexene[5] provided (70% yield) the keto ester **3**[6] (Scheme I), accompanied by a small amount of O-alkylation product.[7] As expected,[4] the sole C-alkylation product was that derived from approach of the alkylating agent from the side of the enolate anion opposite to the secondary methyl group. Efficient conversion of compound **3** into the diene **4** was accomplished by a one-pot sequence of reactions involving conversion of **3** into the corresponding enol trifluoromethanesulfonate,[8] followed by a Pd(0)-catalyzed intramolecular coupling process.[5,9]

A Diels–Alder reaction of the diene **4** with propenal, followed by equilibration (NaOMe, MeOH) of the resultant mixture of four adducts,[10] provided a mixture of the two aldehydes **5** and **8** in a ratio of ≈3:7, respectively. Clean separation of **5** and **8** by flash chromatography[11] on silica gel afforded the two pure substances in yields of 29 and 58%, respectively. Conversion of **8** into **9** was accomplished efficiently by known methodology, in which reductive displacement of a primary (*p*-tolylsulfonyl)oxy group with lithium triethylborohydride[12] played a key role.

Introduction of a necessary functional group at C-11 (amphilectane numbering) of the intermediate **9** was effected smoothly by an allylic oxidation with CrO_3–3,5-dimethylpyrazole.[13] Reduction of the resultant α,β-unsaturated ketone **10** (mp 53–54 °C) with sodium in ammonia containing 2.3 equiv of Me_3COH[14] produced a single product **11** (mp 79–81 °C) in high yield. Stereochemically, this reduction would be expected to produce the product in which the six-membered rings are trans-fused, and, therefore, the relative configuration of **11** could be assigned with confidence. Treatment of the ketone **11** with a reagent derived from zinc dust, CH_2Br_2, and $TiCl_4$[15] provided the required alkene **12** (mp 45–48 °C).

The correct stereochemistry at C-1 was introduced by epimerization of the axially oriented formyl group in compound **13** (mp 68–70 °C), which was readily derived from **12**. Subjection of the epimeric aldehyde **14** (mp 65–67 °C) to a Wittig–Horner reaction with the potassium salt of trimethyl 2-phosphonopropionate gave, after column chromatography on silica gel, the geometrically isomeric α,β-unsaturated esters **15** (77% yield, mp 106–108 °C) and **16** (19% yield, mp 101–103 °C). Treatment of **15** with sodium benzeneselenoate in refluxing THF–hexamethylphosphoramide (HMPA)[16] (78 h)[17] gave the dicarboxylic

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(6) All compounds reported herein exhibited spectra consistent with assigned structures and gave satisfactory molecular mass determinations (high-resolution mass spectrometry). The purity of all compounds was established to be ≥95% by ^1H NMR, TLC, and/or GLC analyses.
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(10) On the basis of earlier work[5] on the Diels–Alder reactions of dienes structurally similar to **4**, the structures of the four adducts (relative proportions ≈ 28:2:62:8) could be assigned as **5**, **6**, **7**, and **8**, respectively. As expected,[5] base-catalyzed equilibration converted **6** and **7** into **5** and **8**, respectively.
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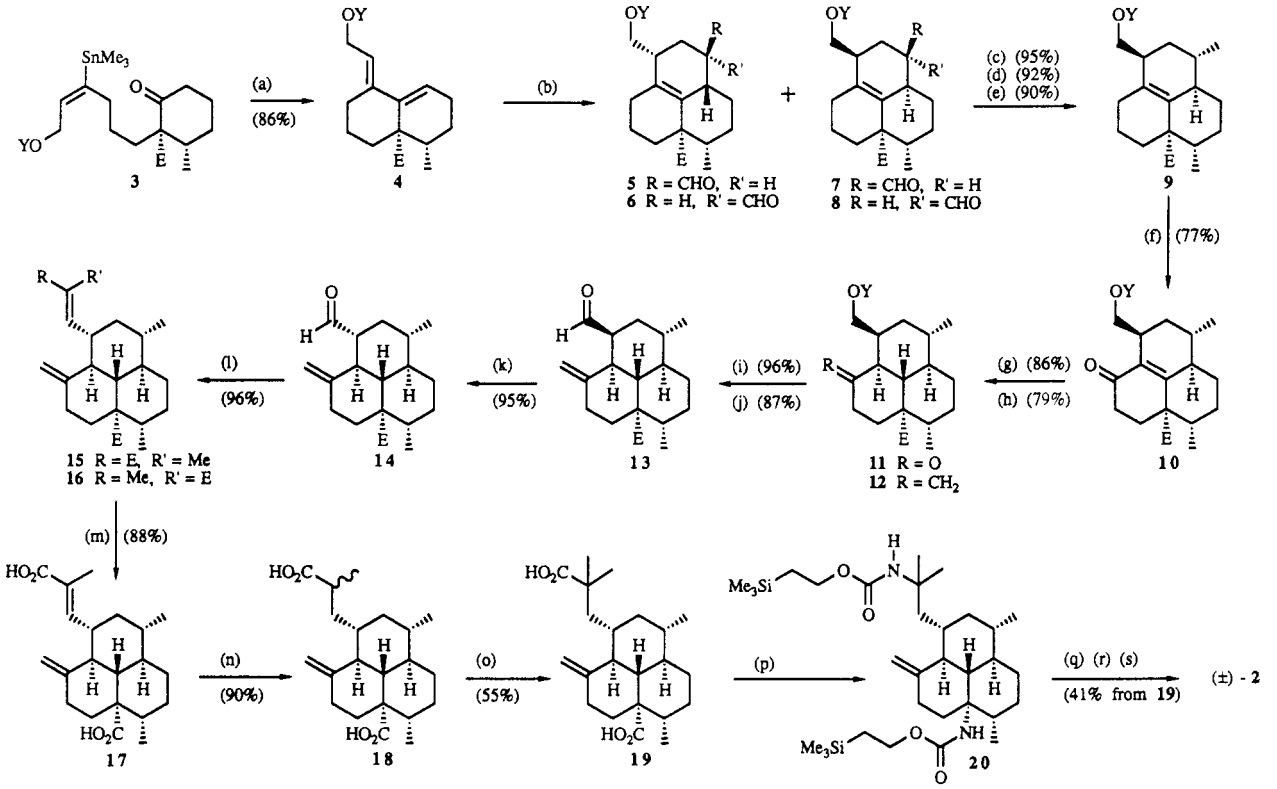
0022-3263/89/1954-1483$01.50/0

Scheme I[a]



[a] Y = Si(*t*-Bu)Me_2, E = CO_2Me; (a) LiN(*i*-Pr)$_2$, THF, −48 °C, 1 h; $PhN(SO_2CF_3)_2$, room temperature, 30 min; $(Ph_3P)_4Pd$ (0.07 equiv), reflux overnight; (b) propenal, PhH, reflux, 20 h; NaOMe, MeOH; (c) $NaBH_4$, MeOH; (d) *p*-$MeC_6H_4SO_2Cl$, pyridine, *p*-(*N*,*N*-dimethylamino)pyridine, CH_2Cl_2; (e) $LiEt_3BH$, THF, room temperature, 3 h; NaOH, H_2O_2, H_2O, THF; (f) CrO_3–3,5-dimethylpyrazole, CH_2Cl_2, 0 °C, 1.5 h; (g) Na, *t*-BuOH, refluxing NH_3, 40 min; (h) Zn, CH_2Br_2, $TiCl_4$, CH_2Cl_2, room temperature, 30 min; (i) *n*-Bu_4NF, THF, room temperature, 4 h; (j) $(COCl)_2$, Me_2SO, CH_2Cl_2, −78 °C; Et_3N, −78 °C to room temperature; (k) NaOMe, MeOH; (l) $[(MeO)_2POC(Me)CO_2Me]K$, THF, 18-crown-6, room temperature; (m) PhSeNa, THF, HMPA, reflux, 78 h; H_3O^+; (n) Li, refluxing NH_3, 30 min; H_3O^+; (o) LiN(*i*-Pr)$_2$ (~10 equiv), THF, room temperature, 2.5 h; MeI (excess), room temperature, 1 h; H_3O^+; (p) $(PhO)_2PON_3$, Et_3N, PhMe, 80 °C, 2 h; $Me_3SiCH_2CH_2OH$, Et_3N, PhMe, 100 °C, 60 h (after 20 and 40 h, additional amounts of $Me_3SiCH_2CH_2OH$ and Et_3N were added); (q) *n*-Bu_4NF, THF, 50 °C, 2 h; (r) AcOCHO, Et_2O, room temperature, 2 h; (s) Ph_3P, CCl_4, Et_3N, CH_2Cl_2, 55 °C, 6.5 h.

acid **17** (mp 273–275 °C), which, upon reduction with lithium in ammonia,[18] afforded the diacid **18** (mixture of epimers).[19] Treatment of **18** with an excess of lithium diisopropylamide in THF, followed by alkylation of the resultant trianion with MeI, gave the required diacid **19** (mp 245–247 °C).

Completion of the total synthesis of (±)-**2** required the degradation of the carboxyl groups of **19** to isonitrile functions. These synthetic operations were carried out simultaneously. Thus, compound **19** was converted into the dicarbamate **20** (colorless oil, IR 1731 cm^{-1}) via a one-pot sequence of two transformations involving treatment of **19** with diphenyl phosphorazidate and triethylamine[20] in PhMe (80 °C), followed by reaction of the resultant diisocyanate (IR 2170 cm^{-1}) with 2-(trimethylsilyl)ethanol[21] in the presence of triethylamine in the same solvent (100 °C). Reaction of **20** with tetra-*n*-butylammonium fluoride in warm THF,[21] followed by treatment of the resultant diamine with acetic formic anhydride in diethyl ether,[22] gave the corresponding diformamide. This material, which consisted of a mixture of rotamers associated with the amide functions, was allowed to react with triphenylphosphine–carbon tetrachloride in the presence of triethylamine.[23] The resultant crystalline product, (±)-8,15-diisocyano-11(20)-amphilectene (**2**), was spectrally identical with the natural product (−)-**2**.[24] Racemic **2** exhibited mp 84–86 °C: IR 2127 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.78–0.94 (m, 2 H), 0.92 (d, 3 H, *J* = 6 Hz), 1.00 (d, 3 H, *J* = 6 Hz), 1.02–1.15 (m, 2 H), 1.20–1.50 (m, 4 H), 1.45 (t, 3 H, *J* = 2 Hz), 1.47 (t, 3 H, *J* = 2 Hz), 1.54 (m, 2 H), 1.85 (t, 1 H, *J* = 11 Hz), 1.93–2.04 (m, 2 H), 2.09 (dd, 1 H, *J* = 15, 2 Hz), 2.23–2.36 (m, 4 H), 4.68 (s, 1 H), 4.87 (s, 1 H); ^{13}C NMR (C_6D_6, 75 MHz) δ 15.9, 19.9, 30.0, 30.2, 30.5, 31.5, 33.5, 33.9, 35.6, 39.7, 40.9, 41.2, 42.9, 45.7, 46.3, 55.5, 56.5 (t, *J* = 4 Hz), 66.9 (t, *J* = 4 Hz), 106.6, 150.0, 158.1 (t, *J* = 4 Hz), 159.9 (t, *J* = 4 Hz).

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Edward Piers,* Montse Llinas-Brunet
Department of Chemistry
University of British Columbia
Vancouver, British Columbia
Canada V6T 1Y6
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(17) With shorter reaction times, it is possible to effect chemoselective cleavage of the α,β-unsaturated ester function.
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