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Total Synthesis of Amphilectane-Type Diterpenoids: (±)-8-Isocyano-10,14-amphilectadiene

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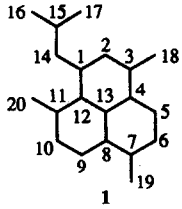
Abstract: A total synthesis of the amphilectane-type diterpenoid (±)-8-isocyano-10,14-amphilectadiene (**3**), starting from the previously reported tricyclic ketone **6**, is described. The key transformations of a six-step conversion of **6** into the alkene **16** involved stereoselective reduction of **6** to give the alcohol **11**, clean base-catalyzed isomerization of the aldehyde **14** to provide the epimer **15**, and a Wittig reaction of **15** with $Ph_3P{=}CMe_2$ to produce **16**. The ketone **18**, readily derived from **16**, was converted, via reaction of the corresponding vinyl trifluoromethanesulfonate (triflate) **19** with Me_2CuLi, into the diene **20**. Efficient degradation of the CO_2Me group in **20** to the isonitrile function completed the synthesis of the natural product **3**.

INTRODUCTION

The small family of amphilectane-type diterpenoids, which share the structurally interesting tricyclic carbon skeleton **1**, have been isolated from marine sponges.[1-3] The first member of this group of natural products to be structurally characterized, (-)-8,15-diisocyano-11(20)-amphilectene, was obtained from *Hymeniacidon amphilecta* and was shown on the basis of an X-ray crystallographic study to possess the constitution and *relative* configuration shown in formula **2**.[1] Subsequently characterized [1-3] substances belonging to this class included (-)-8-isocyano-10,14-amphilectadiene, which was isolated from the Palauan sponge *Halichondria sp.* and was determined to have the structure (relative stereochemistry only) depicted in **3**.[3] Both **2** and **3**, as well as other members of the amphilectane family of diterpenoids, exhibit notable antimicrobial activity. For example, **2** and **3** inhibit the growth of *Staphylococcus aureus* and *Bacillus subtilis*.



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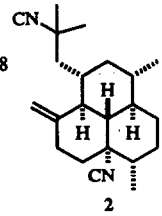

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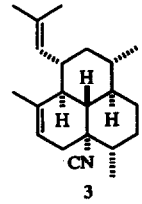

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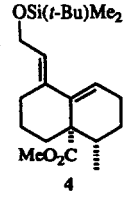

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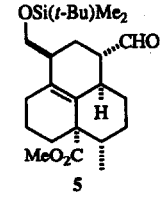

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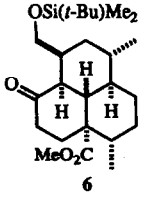
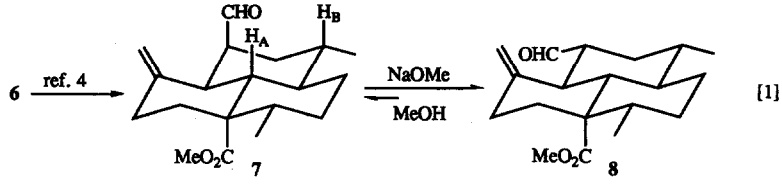


6

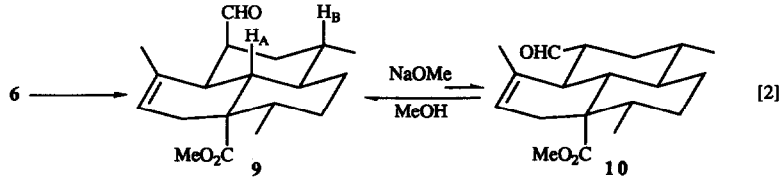
Previous work in this laboratory culminated in a total synthesis of racemic **2**.[4] A key transformation in this synthesis involved a completely regioselective Diels-Alder reaction of the structurally novel diene **4** with acrolein. This cycloaddition process, along with base-catalyzed equilibration of the initially formed product mixture, produced the aldehyde **5** as the predominant product.[4] Suitable functional group manipulations served to convert **5** into the substituted tricyclic ketone **6**, which was transformed into (±)-**2** via a twelve-step sequence of reactions. We report in this paper a total synthesis of (±)-8-isocyano-10,14-amphilectadiene (**3**), starting from the ketone **6**.

RESULTS AND DISCUSSION

In the earlier work on the synthesis of (±)-**2**, the correct relative configuration at C-1 (amphilectane numbering, see **1**) was established by base-catalyzed equilibration of the olefinic aldehyde **7**, which was readily derived from the ketone **6**[4] (see eq. [1]). In compound **7**, the formyl group is axially oriented and thus experiences 1,3-*syn*-axial steric interactions with H_A and H_B. On the other hand, in the epimeric substance **8**, steric repulsions involving the CHO function are minimal. Consequently, it is not surprising that, upon treatment with sodium methoxide in methanol, **7** was converted cleanly and efficiently into the (desired) intermediate **8**.[4]



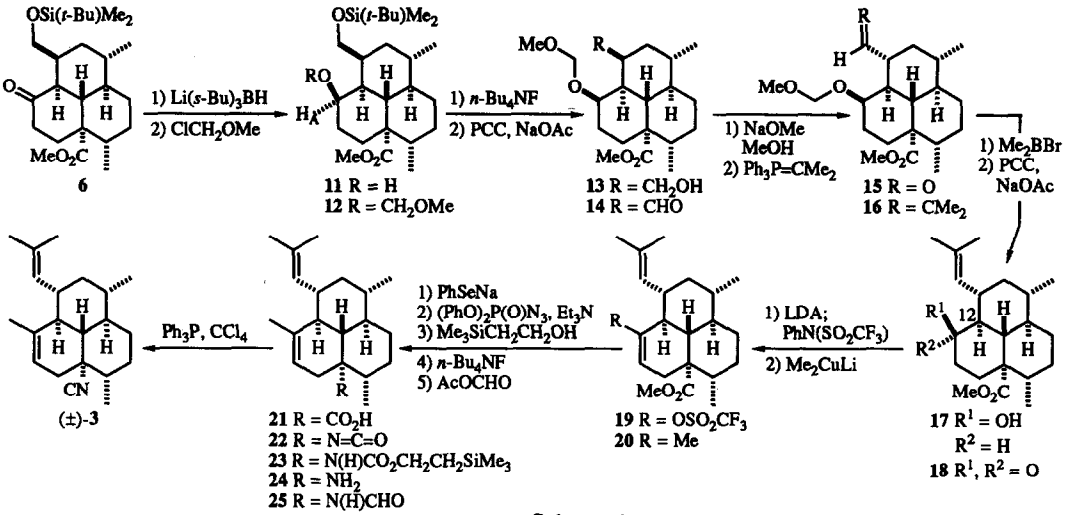
[1]



[2]

The situation involving compound **9**, the endocyclic double bond isomer of **7**, is quite different (eq. [2]). Molecular models show that, in the aldehyde **10**, there is a notable steric repulsion between the vinyl methyl group and the formyl function. Thus, at the outset of the present synthetic work, it was not clear that the required (relative) configuration at C-1 of the amphilectane skeleton could be secured by epimerization of **9**. In practice, this anticipated problem turned out to be real. Thus, although the aldehyde **9** could be obtained efficiently from the ketone **6** via a sequence of reactions based on known methodology, treatment of the former substance with sodium methoxide in methanol gave back only starting material. Essentially none of the epimeric substance **10** could be detected in the crude isolated material. Apparently, the steric repulsions inherently present in **9** (*syn*-axial interactions between CHO and H_A and H_B) are less destabilizing than the repulsion between the vinyl methyl and formyl groups in **10**, with the result that **9** is more stable than **10**. Consequently, an alternative route that would allow control of the configuration at C-1 had to be developed.

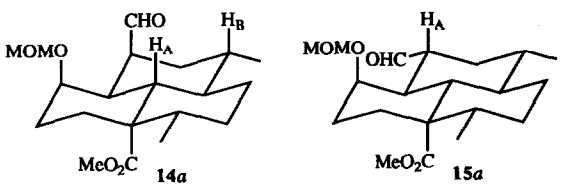
Reduction of the ketone **6** with lithium tri-*sec*-butylborohydride in tetrahydrofuran (THF)[5] provided the alcohol **11** (Scheme 1). The fact that the latter substance contained, as expected,[5] an axially oriented hydroxyl



Scheme 1

group was confirmed by ^{1}H NMR spectroscopy. In the spectrum of **11**, the resonance due to H_A appears as a "broad singlet" with a width-at-half-height of ~7.5 Hz, clearly showing that H_A is equatorial. Reaction of **11** with chloromethyl methyl ether in acetonitrile in the presence of diisopropylethylamine and a catalytic amount 4-(*N*,*N*-dimethylamino)pyridine[6] afforded the methoxymethyl (MOM) ether **12** (>90% from **6**).

Cleavage of the *tert*-butyldimethylsilyl ether by reaction of **12** with tetra-*n*-butylammonium fluoride (TBAF) in THF,[7] followed by oxidation of the resultant primary alcohol **13** with pyridinium chlorochromate (PCC) in the presence of sodium acetate[8] provided the aldehyde **14**. In compound **14**, the CHO and OMOM functions are in a 1,3-diaxial relationship (see conformational formula **14***a*). The resultant steric repulsion, along with the 1,3-*syn*-axial interactions between the formyl group and the protons H_A and H_B (see **14***a*), ensures that this intermediate is considerably less stable than the (desired) epimeric substance **15** (see **15***a*). Indeed, treatment of crude **14** with sodium methoxide in methanol produced cleanly the aldehyde **15** (74% from the alcohol **13**). In a decoupling experiment (^{1}H NMR spectroscopy, compound **15**), irradiation at δ 9.58 (doublet, J = 3.5 Hz, CHO proton) changed the multiplet (δ 2.71-2.61) due to H_A (see **15***a*) to a doublet of doublet of doublets with coupling constants of approximately 12, 11.5 and 3.5 Hz. Thus, it is clear that, in compound **15**, the CHO function and its geminal partner H_A are equatorial and axial, respectively.



Wittig olefination of the aldehyde **15** with isopropylidenetriphenylphosphorane in dimethyl sulfoxide[9] provided the ether alkene **16**. Although the yield of this reaction was variable (~65-90%), this method was generally superior to those involving preparation of the phosphorane by reaction of isopropyltriphenylphos-

phonium bromide with potassium *tert*-amylate in benzene[10] or with *n*-butyllithium in hexane-ether.[11] The ^{1}H NMR spectrum of **16** exhibits a broad doublet (J = 10 Hz) at δ 4.89 due to the olefinic proton and two three-proton doublets (J = 1 Hz) at δ 1.66 and 1.59 derived from the vinyl methyl groups. In a decoupling experiment, irradiation at δ 4.89 caused collapse of the doublets at 1.66 and 1.59 to sharp singlets.

At this stage of the synthesis, the MOMO$^-$ function, which had served its purpose in "forcing" the aldehyde **14** to undergo base-catalyzed epimerization to the required aldehyde **15**, had to be converted back to a carbonyl group. To that end, cleavage of the MOM ether was effected by treatment of **16** with dimethylboron bromide in dichloromethane at -78°C.[12] Since the resultant alcohol **17** turned out to be quite unstable, it was immediately converted, via oxidation (PCC, NaOAc), into the required ketone **18**. In the ^{1}H NMR spectrum of **18**, the axially oriented proton on C-12 appears as a doublet of doublets (J = 11.5, 10 Hz) at δ 2.27.

Conversion of the ketone **18** into the diene **20** was conveniently accomplished by means of effective methodology developed by McMurry and Scott. Thus, reaction of the lithium enolate of **18** with *N*-phenyltrifluoromethanesulfonimide in THF-hexamethylphosphoramide (HMPA)[13] afforded the vinyl triflate **19** in 52% yield. Treatment of the latter substance with an excess of lithium dimethylcuprate[14,15] in diethyl ether at -10° C provided an excellent yield of the diene **20**. The ^{1}H NMR spectrum of **20** displays two one-proton signals (δ 5.37, 5.09) due to the olefinic protons and three three-proton resonances (δ 1.63, 1.60, 1.56) derived from the vinyl methyl groups.

Conversion of the intermediate **20** into the target compound **3**, which required degradation of the ester group into an isonitrile function, was accomplished efficiently via use of a sequence of reactions very similar to that employed in earlier work on the synthesis of (±)-**2**.[4] Treatment of **20** with the highly nucleophilic sodium phenyl selenide in THF-HMPA[16] provided the crystalline carboxylic acid **21**. Reaction of the latter material with diphenylphosphorazidate and triethylamine[17] in warm (80°C) toluene, followed by treatment (toluene, 90°C) of the resultant isocyanate **22** with 2-(trimethylsilyl)ethanol and triethylamine,[18] gave, in high yield, the carbamate **23**. The ^{1}H NMR spectrum of **23** displays signals at δ 4.27 (1 H, broad singlet), 4.13-4.02 (2 H, multiplet), and 0.03 (9 H, singlet) due to the N-H, -CO_2CH_2- , and Me_3Si protons, respectively.

Cleavage of the carbamate function was achieved by treatment of **23** with TBAF in warm THF.[18] The resultant primary amine **24**, upon reaction with acetic formic anhydride in diethyl ether,[19] provided the formamide **25**. Treatment of the latter substance with triphenylphosphine-carbon tetrachloride in the presence of triethylamine[20] gave, in 80% yield from the carbamate **23**, (±)-8-isocyano-10,14-amphilectadiene (**3**). The ^{1}H NMR spectrum of this crystalline material (mp 79-81°C) is essentially identical with that of natural (-)-**3**.[21] Furthermore, the data derived from the ^{13}C NMR spectrum of (±)-**3** agrees very well with those reported for the natural product.[3]

CONCLUSION

Overall, the synthetic efforts summarized above resulted in an efficient conversion of the previously reported[4] intermediate **6** into (±)-8-isocyano-10,14-amphilectadiene (**3**). To our knowledge, this work represents the first reported total synthesis of this structurally and biologically interesting natural product.

EXPERIMENTAL

General Information. Distillation temperatures, which refer to bulb-to-bulb (Kugelrohr) distillations, and melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on $CDCl_3$ solutions. Proton signal positions for compounds containing trialkylsilyl groups are given relative to that for $CHCl_3$ (δ 7.25), while carbon chemical shifts are given relative to that for $CDCl_3$ (δ 77.0). Flash chromatography[22] was carried out with 230-400 mesh silica gel (E. Merck). TLC analyses were done with commercial aluminum-backed silica gel plates. GLC analyses were performed on instruments equipped with flame ionization detectors and 25 m x 0.21 mm fused silica columns coated with cross-linked SE-54. Reagents and solvents were purified and dried using standard methods. Aqueous NH_4Cl-NH_4OH (pH 8) refers to a solution prepared by addition of ~50 mL of aqueous NH_4OH (28-30%) to ~950 mL of saturated aqueous NH_4Cl.

Note: All reactions, unless otherwise noted, were carried out under an atmosphere of dry argon using oven- or flame-dried glassware.

Preparation of the Alcohol 11. To a cold (-78°C), stirred solution of the ketone **6** (60 mg, 0.14 mmol) in dry THF (3.3 mL) was added a solution of Li(*s*-Bu)$_3$BH in THF (1 M, 0.2 mL, 0.2 mmol). The mixture was stirred at -78°C for 3 h and at 0°C for 1 h. Aqueous NaOH (10%, 0.5 mL) and aqueous H_2O_2 (30%, 0.33 mL) were added and the mixture was stirred at room temperature for 5 h. Water (20 mL) and Et_2O (20 mL) were added and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 25 mL) and the combined extracts were washed (5% aqueous $NaHSO_3$, 20 mL; brine, 2 x 20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (10 g silica gel, 9:1 pentane-Et_2O) of the residual material afforded 59 mg (98%) of the alcohol **11**, a colorless oil that displayed IR (neat) 3453, 1724, 1256, 1170, 1072 cm^{-1}; ^1H NMR (400 MHz) δ 5.26 (br s, 1 H, exchanges with D_2O), 4.10 (dd, 1 H, J = 9.5, 11 Hz), 3.91 (br s, 1 H, $w_{1/2}$ = 7.5 Hz after addition of D_2O), 3.66 (s, 3 H), 3.49 (br d, 1 H, J = 11 Hz), 2.16 (ddd, 1 H, J = 13, 3.5, 3.5 Hz), 2.00-1.86 (m, 3H), 1.84-1.76 (m, 2 H), 1.70-1.61 (m, 2 H), 1.59-1.10 (diffuse m, 6 H), 0.96 (d, 3 H, J = 7 Hz), 0.93-0.80 (diffuse m, 5 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H). *Exact mass* calcd. for $C_{24}H_{42}O_3Si$ (M^+-H_2O): 406.2903; found: 406.2903.

Preparation of the Methoxymethyl Ether 12. To a stirred solution of the alcohol **11** (279 mg, 0.60 mmol) in dry CH_3CN (7 mL) were added sequentially *i*-Pr_2NEt (0.47 mL, 2.7 mmol), 4-(*N*,*N*-dimethylamino)pyridine (3 mg, 0.03 mmol) and $MeOCH_2Cl$ (0.2 mL, 2.6 mmol). The mixture was refluxed for 5 h, was cooled to room temperature, and then was concentrated. Et_2O (40 mL) and saturated aqueous $NaHCO_3$ (20 mL) were added to the residual material, the phases were separated, and the aqueous layer was extracted with Et_2O (2 x 40 mL). The combined extracts were washed (brine, 2 x 40 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (45 g silica gel, 9:1 pentane-Et_2O) of the crude product provided 295 mg (96%) of the ether **12**, a colorless oil that exhibited IR (neat) 1724, 1082, 1045 cm^{-1}; ^1H NMR (400 MHz) δ 4.65 (s, 2 H), 3.87 (dd, 1 H, J = 10.5, 5.5 Hz), 3.72 (br s, 1 H, $w_{1/2}$ = 7.5 Hz), 3.66 (s, 3 H), 3.61 (dd, 1 H, J = 10.5, 10.5 Hz), 3.39 (s, 3 H), 2.18 (m, 1 H), 2.05-1.78 (diffuse m, 5 H), 1.58-1.13 (diffuse m, 8 H), 0.93 (d, 3 H, J = 6.5 Hz), 0.90 (s, 9 H), 0.86 (d, 3 H, J = 6.5 Hz), 1.07-0.80 (m, 2 H), 0.03 (s, 3 H), 0.02 (s, 3 H). *Exact mass* calcd. for $C_{24}H_{43}O_4Si$ (M^+-C_2H_5O): 423.2931; found: 423.2932.

Preparation of the Alcohol 13. To the diether **12** (85 mg, 0.18 mmol) was added a solution of *n*-Bu_4NF in THF (1 M, 2.44 mL, 2.44 mmol) and the mixture was stirred at room temperature for 5 h. Saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with Et_2O (3 x 2 mL). The combined extracts were washed (brine, 2 x 20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (14 g silica gel, 7:3 Et_2O-petroleum ether) of the remaining oil afforded 62 mg (96%) of the alcohol **13**, a colorless oil that showed IR (neat) 3417, 1723, 1039 cm^{-1}; ^1H NMR (400 MHz) δ 4.70, 4.68 (d, d, 1 H each, J = 4 Hz in each case), 3.88 (br s, 1 H), 3.85 (m, 1 H, transformed to a dd, J = 12, 6 Hz, upon addition of D_2O), 3.68 (s, 3 H), 3.59 (ddd, 1 H, J = 12, 7, 4 Hz, transformed to a dd, J = 12, 4 Hz, upon addition of D_2O), 3.44 (s, 3 H), 3.20 (t, 1 H, J = 7 Hz, exchanges with D_2O), 2.24-2.15 (m, 1 H), 2.09 (ddd, 1 H, J = 13, 6, 3 Hz), 2.04-1.94 (m, 2 H), 1.92-1.74 (m, 2 H), 1.71-1.15 (diffuse m, 9 H), 0.95 (d, 3 H, J = 7 Hz), 1.01-0.82 (m, 1 H), 0.85 (d, 3 H, J = 6 Hz). *Exact mass* calcd. for $C_{20}H_{34}O_5$: 354.2406; found: 354.2408.

Preparation of the Aldehyde 15. To a stirred slurry of PCC (280 mg, 1.3 mmol) and anhydrous NaOAc (28 mg, 0.6 mmol) in dry CH_2Cl_2 (9 mL) at room temperature was added a solution of the alcohol **13** (218 mg, 0.62 mmol) in dry CH_2Cl_2 (2 mL) and the mixture was stirred for 2 h. Dry Et_2O (10 mL) was added and the mixture was passed through a column of Florisil (20 g, elution with Et_2O). The eluate was concentrated and the remaining crude material (the aldehyde **14**) was dissolved in dry MeOH (3.5 mL). A solution of NaOMe in dry MeOH (0.2 M, 0.3 mL) was added and the solution was stirred at room temperature for 6.5 h. The mixture was concentrated and Et_2O (30 mL) and saturated aqueous NH_4Cl (10 mL) were added to the residue. The phases were separated, the aqueous layer was extracted with Et_2O (2 x 30 mL), and the combined extracts were washed (brine, 30 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (35 g silica gel, 7:3 petroleum ether-Et_2O) to produce 161 mg (74%) of the aldehyde **15**, a colorless oil that exhibited IR (neat): 2704, 1724, 1377, 1042 cm^{-1}; ^1H NMR (400 MHz) δ 9.58 (d, 1 H, J = 3.5 Hz), 4.65 (d, 1 H, J = 7 Hz), 4.56 (d 1 H, J = 7 Hz), 3.69 (br s, 4 H), 3.37 (s, 3 H), 2.71-2.61 (m, 1 H), 2.31-2.24 (m, 1 H), 2.07-1.84 (diffuse m, 3 H), 1.73 (dd, 1 H, J = 10, 3.5 Hz), 1.55-1.02 (diffuse m, 9 H), 0.94 (d, 3 H, J = 6 Hz), 0.91 (d, 3H, J = 7 Hz), 0.98-0.83 (m, 1 H). In decoupling experiments, irradiation at δ 9.58 caused collapse of the m at 2.71-2.61 to a ddd ($J \approx$ 12, 11.5, 3.5 Hz), while saturation at δ 2.67 caused collapse of the d at δ 9.58 to a s, simplified the multiplets at 2.07-1.84 and 1.55-1.02, and changed the dd at 1.73 to a d (J = 10 Hz). *Exact mass* calcd. for $C_{19}H_{28}O_4$ (M^+-CH_4O): 320.1987; found: 320.1990.

Preparation of the Alkene 16. To a stirred solution of CH_3SOCH_2Na (0.7 mmol) in dry Me_2SO (7 mL) was added, in small portions, solid $Ph_3P(i\text{-}Pr)Br$ (278 mg, 0.72 mmol, recrystallized from pentane-CH_2Cl_2 and dried (vacuum pump) overnight) and the dark red mixture was stirred at room temperature for 15 min. A solution of the aldehyde **15** (62 mg, 0.16 mmol) in dry Me_2SO (2 mL) was added and stirring was continued for 2 h. Water (40 mL) was added and the mixture was extracted with 1:1 pentane-Et_2O (2 x 40 mL). Solid NaCl was added to the aqueous phase, which was then extracted with 1:1 pentane-Et_2O (40 mL) and pentane (40 mL). The combined organic extracts were washed (water, 5 x 20 mL; brine 2 x 20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (10 g silica gel, 92:8 petroleum ether-Et_2O) of the crude product provided 50 mg (75%) of the alkene **16**, a colorless oil that showed IR (neat) 1725, 1376, 1171, 1147, 1045 cm^{-1}; ^1H NMR (400 MHz) δ 4.89 (br d, 1 H, J = 10 Hz), 4.63 (d, 1 H, J = 6 Hz), 4.53 (d, 1 H, J = 6 Hz), 3.67 (s, 3 H), 3.65 (br s, 1 H, $w_{1/2}$ = 8 Hz), 3.35 (s, 3 H), 2.45-2.24 (diffuse m, 2 H), 2.05-1.80 (diffuse m, 4 H),

1.66 (d, 3 H, J = 1 Hz), 1.59 (d, 3 H, J = 1 Hz), 1.58-1.18 (diffuse m, 9 H), 0.98-0.80 (m, 1H), 0.90 (d, 3 H, J = 7 Hz), 0.86 (d, 3 H, J = 7 Hz). In a decoupling experiment, irradiation at δ 4.89 caused collapse of the doublets at 1.66 and 1.59 to singlets. *Exact mass* calcd. for $C_{23}H_{38}O_4$: 378.2770; found: 378.2765.

Preparation of the Keto Alkene 18. To a cold (-78°C), stirred solution of the alkene **16** (62 mg, 0.16 mmol) in dry CH_2Cl_2 (1.5 mL) was added a solution of Me_2BBr in dry CH_2Cl_2 (1.3 M, 0.15 mL, 0.19 mmol) and the solution was stirred at -78°C for 20 min. Saturated aqueous $NaHCO_3$ (1 mL) and THF (2.1 mL) were added simultaneously and the mixture was warmed to room temperature. Brine (5 mL) and Et_2O (5 mL) were added, the phases were separated, and the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined extracts were washed (brine, 5 mL), dried ($MgSO_4$), and concentrated. The crude product (the alcohol **17**) was dissolved in dry CH_2Cl_2 (1 mL) and the solution was added, using a cannula (washing with 0.5 mL of dry CH_2Cl_2), to a stirred slurry of PCC (95 mg, 0.44 mmol) and anhydrous NaOAc (12 mg, 0.146 mmol) in dry CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 2 h. Et_2O (3 mL) was added and the suspension was filtered through a column of Florisil (10 g, elution with Et_2O). Concentration of the eluate, followed by flash chromatography of the residual material on silica gel (11 g, 9:1 pentane-Et_2O) produced 46 mg (85%) of the keto alkene **18**, a white solid that exhibited mp 91-93°C (from Et_2O-pentane); IR (KBr) 1724, 1717, 1375 cm^{-1}; ^1H NMR (400 MHz) δ 4.67 (br d, 1 H, J = 9 Hz), 3.77 (s, 3 H), 2.82 (ddd, 1 H, J = 13.5, 6, 3 Hz), 2.65-2.53 (m, 1 H), 2.48 (ddd, 1 H, J = 13.5, 13.5, 6 Hz), 2.33-2.29 (m, 1 H), 2.27 (dd, 1 H, J = 11.5, 10 Hz), 1.06 (dq, 1 H, J = 13.5, 3.5 Hz), 2.01-1.90 (m, 1 H), 1.73 (d, 3 H, J = 1.5 Hz), 1.62 (d, 3 H, J = 1 Hz), 1.57-1.24 (diffuse m, 7 H), 1.17 (dd, 1 H, J = 12.5, 11.5 Hz), 0.93 (d, 3 H, J = 7 Hz), 0.88 (d, 3 H, J = 6 Hz), 0.97-0.78 (m, 1 H). *Exact mass* calcd. for $C_{21}H_{32}O_3$: 332.2351; found: 332.2344.

Preparation of the Vinyl Triflate 19. To a cold (-48°C), stirred solution of LDA (0.56 mmol) in dry THF (1.1 mL) was added a solution of the ketone **18** (46 mg, 0.14 mmol) in dry THF (0.5 mL) and the mixture was stirred for 1 h. A solution of $PhN(SO_2CF_3)_2$ (150 mg, 0.42 mmol) and dry HMPA (25 μL, 0.14 mmol) in dry THF was added. The solution was stirred at -48°C for 15 min and at room temperature for 30 min, and then was poured into rapidly stirred saturated aqueous $NaHCO_3$ (15 mL). The mixture was extracted with pentane (3 x 20 mL) and the combined extracts were washed (brine, 2 x 10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (8 g silica gel, pentane, then 97:3 pentane-Et_2O) of the crude material gave 10 mg of the starting material **18** and 33.5 mg (52%, 67% based on recovered starting material) of the vinyl triflate **19**, a colorless oil that showed IR (neat) 1728, 1207 cm^{-1}; ^1H NMR (400 MHz) δ 5.73 (br d, 1 H, J = 7 Hz), 5.04 (br d, 1 H, J = 8 Hz), 3.64 (s, 3 H), 3.02 (dd, 1 H, J = 18, 7 Hz), 2.36-2.25 (m, 2 H), 2.14-2.06 (m, 1 H), 1.87-1.78 (m, 1 H), 1.66 (d, 3 H, J = 1 Hz), 1.57 (d, 3 H, J = 1 Hz), 1.57-1.35 (diffuse m, 5 H), 1.30-1.20 (m, 2 H), 1.18-0.96 (diffuse m, 2 H), 0.90 (d, 3 H, J = 7 Hz), 0.88 (d, 3 H, J = 6 Hz). *Exact mass* calcd. for $C_{22}H_{31}F_3O_5S$: 464.1844; found: 464.1852.

Preparation of the Diene 20. A solution of the vinyl triflate **19** (66 mg, 0.14 mmol) in dry Et_2O (0.5 mL) was added to a cold (-10°C) solution of Me_2CuLi (1.4 mmol) in dry Et_2O (4 mL). The mixture was stirred at -10°C for 2 h. Aqueous NH_4Cl-NH_4OH (pH 8, 10 mL) was added and stirring was continued (room temperature) for 1 h. The mixture was extracted with Et_2O (3 x 20 mL) and the combined extracts were washed (brine, 20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (11 g silica gel, 97:3 pen-

tane-Et_2O) of the crude product produced 43 mg (92%) of the diene **20**, a colorless oil that displayed IR (neat) 1726, 1456, 1381 cm^{-1}; ^1H NMR (400 MHz) δ 5.39-5.34 (m, 1 H), 5.09 (br d, 1 H, J = 9 Hz), 3.62 (s, 3 H), 2.83 (br dd, 1 H, J = 17, 6 Hz), 2.20-1.95 (diffuse m, 2 H), 1.88-1.79 (m, 1 H), 1.63 (d, 3 H, J = 1 Hz), 1.60 (br s, 3 H), 1.56 (d, 3 H, J = 1 Hz), 1.18 (dd, 1 H, J = 10.5, 10.5 Hz), 0.88 (d, 3 H, J = 6 Hz), 0.84 (d, 3 H, J = 6.5 Hz), 1.76-1.25, 1.14-0.80 (diffuse multiplets, 9 H). *Exact mass* calcd. for $C_{22}H_{34}O_2$: 330.2559; found: 330.2561.

Preparation of the Acid 21. An 80% dispersion of NaH in mineral oil (50 mg, containing ~40 mg, 1.7 mmol, of NaH) was washed with dry THF (3 x 1 mL) and the remaining solid was covered with dry THF (2.5 mL). The stirred slurry was cooled to 0°C and PhSeH (0.17 mL, 1.6 mmol) and dry HMPA (0.57 mL, 3.3 mmol) were added. The orange colored solution was transferred by cannulation to a solution (room temperature) of the ester **20** (50 mg, 0.15 mmol) in dry THF (1 mL). The stirred mixture was refluxed for 54 h, and then was cooled and concentrated. The residual material was treated with water (2 mL) and 10% hydrochloric acid (2 mL). The mixture was extracted with Et_2O (5 x 15 mL) and the combined extracts were washed (water, 5 x 20 mL; brine, 5 x 20 mL) and concentrated. Flash chromatography (8 g silica gel, 4:1 to 3:2 hexane-Et_2O) of the crude product gave 40.5 mg (85%) of the acid **21**, a white solid (mp 174-176°C, from pentane-Et_2O) that displayed IR (KBr) 3280-2380 (br), 1687, 1444, 1277 cm^{-1}; ^1H NMR (400 MHz) δ 5.45-5.36 (m, 1 H), 5.10 (br d, 1 H, J = 9 Hz), 2.81 (dd, 1 H, J = 17, 6 Hz), 2.21-2.10 (m, 1 H), 2.10-2.01 (m, 1 H), 1.95 (br dd, 1 H, J = 10.5, 10.5 Hz), 1.71 (br d, 1 H, J = 17 Hz), 1.64 (d, 3 H, J = 1 Hz), 1.63 (br s, 3 H), 1.56 (d, 3 H, J = 1 Hz), 1.29-1.18 (m, 1 H), 1.14-1.01 (m, 1 H), 0.93 (d, 3 H, J = 6.5 Hz), 0.87 (d, 3 H, J = 6.5 Hz), 1.67-1.39, 1.01-0.81 (diffuse multiplets, 7 H). In decoupling experiments irradiation at δ 5.40 caused collapse of the signal at 2.81 to a d (J = 17 Hz) and sharpened the doublet at 1.71; irradiation at δ 5.10 changed the resonance at 2.21-2.10 to a ddd (J = 10.5, 10.5, 4 Hz) and altered the doublets at 1.64 and 1.56 to singlets. *Exact mass* calcd. for $C_{21}H_{32}O_2$: 316.2403; found: 316.2403.

Preparation of the Carbamate 23. To a stirred solution of the acid **21** (19 mg, 0.06 mmol) in dry PhMe (0.3 mL) at room temperature were added dry Et_3N (14 μL, 0.1 mmol) and $(PhO)_2P(O)N_3$ (14 μL, 0.07 mmol) and the solution was stirred at 80°C for 23 h. The solution, which contained the isocyanate **22**, was cooled and freshly distilled $Me_3SiCH_2CH_2OH$ (0.1 mL, 0.7 mmol) and dry Et_3N (0.1 mL, 0.72 mmol) were added. After the mixture had been stirred at 90°C for 24 h, additional $Me_3SiCH_2CH_2OH$ (0.1 mL) and dry Et_3N (0.1 mL) were added and heating at 90°C was continued for a further 24 h. The mixture was concentrated and Et_2O (3 mL) was added to the residue. The solution was passed through a plug of silica gel (2 g, elution with Et_2O). Concentration of the eluate and flash chromatography (20 g silica gel, 95:5 pentane-Et_2O) of the residual material gave 25 mg (96%) of the carbamate **23**, a colorless oil that exhibited IR (neat) 3446, 3035, 1736, 1508, 1250, 1224 cm^{-1}; ^1H NMR (400 MHz) δ 5.34 (br d, 1 H, J = 5 Hz), 5.11 (br d, 1 H, J = 9 Hz), 4.27 (br s, 1 H, $w_{1/2}$ = 4 Hz), 4.13-4.02 (m, 2 H), 3.68 (br d, 1 H, J = 16 Hz), 2.31-2.19 (m, 1 H), 2.00 (dddd, 1 H, J = 13, 4, 4, 4 Hz), 1.86-1.77 (m, 1 H), 1.77-1.68 (m, 1 H), 1.68-1.64 (m, 6 H), 1.58 (d, 3 H, J = 1 Hz), 1.53-1.12 (m, 8 H), 1.00-0.85 (m, 2 H), 0.96 (d, 3 H, J = 7 Hz), 0.88 (d, 3 H, J = 7 Hz), 0.80-0.70 (m, 1 H), 0.03 (s, 9 H). *Exact mass* calcd. for $C_{26}H_{45}NO_2Si$: 431.3219; found: 431.3228.

(±)-8-Isocyano-10,14-amphilectadiene (3). To a stirred solution of the carbamate **23** (20 mg, 0.046 mmol) in dry THF (0.9 mL) at room temperature was added a solution of *n*-Bu_4NF in THF (1 M, 0.38 mL, 0.38 mmol). The solution was stirred at 55°C for 2 h. The solvent was removed under reduced pressure. Pentane (6 mL) and a 4:1 mixture of saturated aqueous NH_4Cl and 30% aqueous NH_4OH (3.6 mL) were added to the residue. The phases were separated and the aqueous phase was extracted with pentane (2 x 6 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The residual oil (the amine **24**) was dissolved in Et_2O (0.9 mL) and acetic formic anhydride (75 μL, 0.6 mmol) was added. The solution was stirred at room temperature for 2 h. Water (3 mL) and Et_2O (5 mL) were added and the phases were separated. The aqueous layer was extracted with Et_2O (2 x 6 mL) and the combined extracts were washed (brine, 3 mL), dried ($MgSO_4$), and concentrated. The remaining crude oil (the formamide **25**, IR 1681 cm^{-1}) was dissolved in dry CH_2Cl_2 (0.4 mL, room temperature) and Ph_3P (32 mg, 0.12 mmol), dry CCl_4 (11 μL, 0.1 mmol), and dry Et_3N (43 μL, 0.3 mmol) were added. The mixture was stirred at 55°C for 1 h. The solvent was removed under reduced pressure and the residual material was washed (triturated) several times with 97:3 pentane-Et_2O. The combined washings were concentrated and the crude product was subjected to flash chromatography (5 g silica gel, initial elution with pentane, then the constitution of the eluant was gradually changed to 97:3 pentane-Et_2O). Concentration of the appropriate fractions gave 11 mg (80% from the carbamate **23**) of (±)-8-isocyano-10,14-amphilectadiene (**3**), a white solid (mp 79-81°C, from pentane-Et_2O) that displayed IR (KBr) 2126, 1447, 1379 cm^{-1}; ^1H NMR (400 MHz) δ 5.26 (m, 1 H, $w_{1/2}$ = 11 Hz), 5.15 (br d, 1 H, J = 9 Hz), 2.45 (br dd, 1 H, J = 17, 4.5 Hz), 2.31-2.19 (m, 1 H), 2.12-1.92 (m, 3 H), 1.69 (d, 3 H, J = 1 Hz), 1.66 (d, 3 H, J = 1 Hz), 1.57 (d, 3 H, J = 1 Hz), 1.02 (d, 3 H, J = 6.5 Hz), 0.88 (d, 3 H, J = 6 Hz), 1.78-0.79 (diffuse multiplets, 9 H); ^{13}C NMR (75.3 MHz) δ 15.4, 17.5, 19.5, 25.1, 25.7, 29.1, 29.8, 37.2, 37.9, 40.6, 41.4, 42.1, 43.5, 44.8, 49.5, 63.2 (t, J = 4.5 Hz), 118.8, 126.7, 133.4, 137.6, 154.4 (t, J = 4.5 Hz). *Exact mass* calcd. for $C_{21}H_{31}N$: 297.2457; found: 297.2461.

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