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A New Access to *Trans-Syn-Trans* Perhydrophenanthrenic Systems. Synthesis of (9βH)-8α-Methylpodocarpan-13-one

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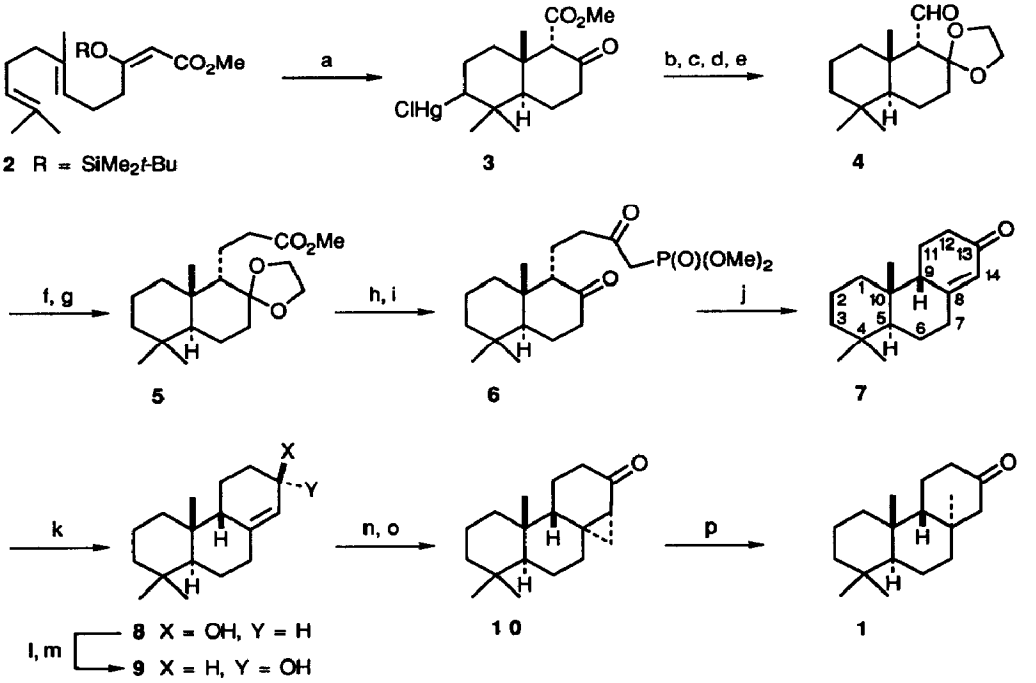
Abstract: (9βH)-8α-Methylpodocarpan-13-one has been synthesized from a 9,10-*syn* bicyclic precursor by a reaction sequence including an intramolecular Horner-Wadsworth-Emmons reaction — to form (9βH)-podocarp-8(14)-en-13-one — and an hydroxy-directed cyclopropanation to introduce the 8-methyl group on the less accessible α side of the molecule.

While working on tricyclohexaprenols,[1] we became interested in the synthesis of perhydrophenanthrenic diterpenes with 9,10-*syn* stereochemistry.[2] Compounds of this type, although much less common in nature than their 9,10-*anti* counterparts, have been isolated from several samples of natural origin and their synthesis has been addressed by several groups in recent years.[3] In this Letter we describe a new access to tetramethylperhydrophenanthrenic ring systems with *trans-syn-trans* stereochemistry (*e. g.*, **1**), a pattern that combines a 9,10-*syn* arrangement with two *trans* ring junctions. It is found in the marine bromo diterpene isoaplysin-20,[4] as well as in triterpenes of the protostane[5] and stictane[6] series, and is remarkable in that the stereochemical arrangement forces the B ring into a boat conformation. Several groups have succeeded in the synthesis of such systems, generating the tricyclic frame either by electrophilic cyclization of open chain precursors,[4bc,7] or stepwise.[8] In recent years the transannular Diels-Alder reaction on macrocyclic precursors has emerged as a powerful method for the synthesis of tricyclic *trans-syn-trans* systems, even though the introduction of a methyl at C-8 is difficult and has, to our knowledge, not been achieved.[9]

We report here a synthesis of the ketone **1** starting from the bicyclic keto ester **3** which was first converted into the tricyclic (9βH)-podocarp-8(14)-en-13-one **7** by a reaction sequence including an intramolecular Horner-Wadsworth-Emmons modification of the Wittig reaction. Whereas podocarp-8(14)-en-13-one – a focal intermediate in many diterpene syntheses – has been prepared in several ways,[10] this is the first synthesis of its epimer **7**. Subsequent transformation of **7** into the allylic alcohol **9** allowed the hydroxy-directed introduction of the 8-methyl on the less accessible α side and gave access to the title compound **1**.

The bicyclic keto ester **3** (mp 205-207 °C), which has been prepared in four steps from geraniol *via* the intermediate **2**,[11] has been choosen as starting material because it not only gives access to the compounds described here but also to their 3-bromo analogues. A preparation of the key intermediate **7** based on Mukaiyama's directed aldol reaction[12] was

first explored but gave only low yields of **7** and of its 7,8-unsaturated isomer. We then contemplated using an intramolecular Wittig reaction provided it could be performed without notable epimerization at C-9 and with the shift of the 8,14-double bond into 7,8 position being kept at a minimum. Since this kind of problem had been dealt with by others, we undertook the preparation of the β-keto phosphonate **6** from the ester **3**. Acetalization with ethylene glycol and chlorotrimethylsilane[13] followed by demercuration with lithium aluminium hydride in tetrahydrofuran (THF), reduction of the methoxycarbonyl with diisobutylaluminium hydride (DIBAH) *in toluene*, and Collins oxidation led to the aldehyde **4** (mp 88-89 °C). The latter when subjected to a Horner-Wadsworth-Emmons olefination with methyl diethylphosphonoacetate and to a catalytic hydrogenation gave the ester **5** which by treatment with lithium methyl dimethylphosphonate and deprotection of the C-8 carbonyl under mild conditions (10% aqueous oxalic acid, silica gel, methylene chloride[14]) led to the β-keto phosphonate **6**. This compound was then treated with



Scheme. a) $Hg(CF_3CO_2)_2$, $MeNO_2$, 0 °C, 1 h; then sat. aq. $NaHCO_3$, sat. aq. NaCl, 1 h; b) Me_3SiCl, $(CH_2OH)_2$, CH_2Cl_2, reflux, 36 h; c) $LiAlH_4$, THF, r. t., 1 h (a-c: 47% yield); d) DIBAH, toluene, 0 °C → r. t., 1 h (95%); e) CrO_3-2 pyridine, CH_2Cl_2, 1 h (88%); f) $(EtO)_2P(O)CHNaCO_2Me$, THF, 24 h (96%); g) H_2, PtO_2, EtOH, 2 h (100%); h) $(MeO)_2P(O)CH_2Li$, THF, –78 °C, 1.5 h (92%); i) 10% aq. $(CO_2H)_2$, SiO_2, CH_2Cl_2 (100%); j) DBU, LiCl, MeCN, 18 h (75%); k) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0.25 h (100%; **8**/**9** 85:15); l) $PhCO_2H$, $EtO_2C–N=N–CO_2Et$, PPh_3, benzene, 0 °C → r. t., 0.5 h; m) DIBAH, toluene, 1 h, –78 °C (l+m: 100%; **8**/**9** 35:65); n) Sm(Hg), ICH_2Cl, –78 °C → r. t., 2 h (88%); o) TPAP, N-methylmorpholine N-oxide, 4A molecular sieves, CH_2Cl_2, 3.5 h (92%); p) Li, $EtNH_2$, *t*-BuOH, –78° C, 0.5 h; then NH_4Cl (79%).

1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and lithium chloride[15] to give the α,β-unsaturated ketone **7** (mp 89-89.5 °C)[16] in up to 75% yield.

Introduction of the 8-methyl on the concave α face of the molecule was then achieved as follows.[17] Reduction of the ketone **7** with sodium borohydride in the presence of cerium chloride[18] led quantitatively to a 85:15 mixture of the alcohols **8** and **9**. When the reduction was performed with lithium tri-*sec*-butylborohydride,[19] the proportion of **9** increased slightly but the yield was lower. We then decided not to test other hydrides but rather to separate the two epimeric alcohols by column chromatography and to transform the 85% of alcohol **8** into the alcohol **9** by a Mitsunobu reaction[20] followed by reduction with DIBAH of the so formed benzoate. This sequence gave us the allylic alcohol **9** (mp 95-96 °C) in 55% yield from ketone **7**, in addition to the 15% already obtained. Hydroxy-directed cyclopropanation of **9** was then best performed with chloroiodomethane and samarium amalgam.[21] After reoxidation of the hydroxy group with tetrapropylammonium perruthenate (TPAP),[22] reduction of the cyclopropyl ketone **10** (mp 93-93.5 °C) with lithium in ethylamine led to the ketone **1** (mp 70.5-72.5 °C).[16] Its stereochemistry could be confirmed by 2D NMR experiments.[23]

The synthesis of a tricyclohexaprenol possessing a *trans-syn-trans* ring system is currently underway in our group.

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16. ^1H- and ^{13}C-NMR data for:
Ketone **7**. δ (^1H, 400 MHz, $CDCl_3$): 0.86 (s, 3 H, Me-4_e), 0.93 (s, 3 H, Me-4_a), 1.02 (dd, *J* 7.1, 12.1 Hz, 1 H, H-5), 1.09 (m, 1 H, H-3_a), 1.21 (s, 3 H, Me-10), 1.35-1.50 (m, 4 H, H-1_a, H-1_e, H-3_e, H-2_e), 1.57 (m, 1 H, H-2_a), 1.62-1.88 [m, 3 H; includes signals centered at 1.68 (H-11_a), 1.78 (2 H-6)], 2.08 (dq, 7 lines, *J* 12.5, 4.3 Hz, 1 H, H-11_e), 2.20 (m, 1 H, H-9), 2.21 (ddd, *J* 16.7, 13.9, 4.6 Hz, 1 H, H-12_a), 2.36 (ddd, *J* 14.9, 9.6, 2.3 Hz, 1 H, H-7), 2.49 (dtd, *J* 16.7, 3.7, 1.1 Hz, 1 H, H-12_e), 2.63 (dddt, 19 lines, *J* 14.9, 11.2, 8.0, 2.1 Hz, 1 H, H-7), 5.83 (br s, 1 H, H-14); δ (^{13}C, 50 MHz, $CDCl_3$): 18.7 (C-2), 20.8 (C-6), 22.4 (Me-4_a), 25.8 (Me-10), 26.0 (C-11), 31.1 (C-7), 32.8 (Me-4_e), 33.6, 37.1 (C-1), 38.2 (C-12), 38.4, 42.4 (C-3), 44.7 (C-5), 51.3 (C-9), 125.8 (C-14), 170.4 (C-8), 199.5 (C-13).
Ketone **1**. δ (^1H, 400 MHz, C_6D_6): 0.82 (s, 3 H, Me-4_e), 0.83 (s, 3 H, Me-4_a), 0.86 (d, *J* 0.6 Hz, 3 H, Me-10), 0.87 (d, *J* 1.1 Hz, 3 H, Me-8), 0.99 and 1.02 (2 m, 2 H, H-1_a and H-3_a), 1.14-1.50 [m, 11 H; includes signals centered at 1.17 (H-1_e), 1.19 (dd, *J* 3.5, 12.7 Hz, H-9), 1.22 (H-6), 1.25 (2 H-7), 1.34 (qd, *J* 13.0, 4.7 Hz, H-11_a), 1.35 (d, *J* 11.1 Hz, H-5), 1.35 (H-3_e), 1.36 (H-2_e), 1.43 (H-6), 1.46 (H-11_e)], 1.55 (m, 1 H, H-2_a), 1.69 (dt, *J* 13.1, 1.1 Hz, 1 H, H-14_a) 1.78 (dddd, 14 lines, *J* 14.3, 13.0, 7.1, 1.0 Hz, 1 H, H-12_a), 2.04 (dd, *J* 13.1, 2.4 Hz, 1 H, H-14_e), 2.28 (ddt, 10 lines, *J* 14.3, 4.7, 2.3 Hz, 1 H, H-12_e); δ (^{13}C, 100 MHz, C_6D_6): 18.0 (C-6), 19.4, 20.1 (C-2), 21.8 (Me-4_a), 23.2 (C-11), 24.0 (Me-10), 24.3 (Me-8), 33.8, 33.9 (Me-4_e), 35.4 (C-1), 37.0, 38.7 (C-7), 41.9 (C-3, C-12), 47.6 (C-5), 52.4 (C-9), 60.2 (C-14), 208.5 (C-13).
The assignments are based on ^1H,^1H-COSY, NOE difference experiments, DEPT, and ^1H,^{13}C-COSY.
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23. The α stereochemistry of the 8-methyl group is confirmed by its coupling with H-14_a (^4J (H,H) 1.1 Hz) and by NOEs from Me-8 to H-5, Me-8 to H-14_e (but not to H-14_a), Me-10 to H-9 (but not from Me-8 to H-9). These effects were shown by NOESY and NOE difference experiments at 400 MHz in C_6D_6.

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