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Periplanone Total Synthesis via Intramolecular Pinacol Coupling

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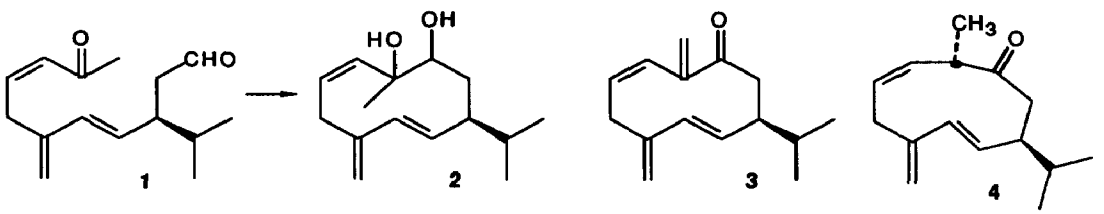
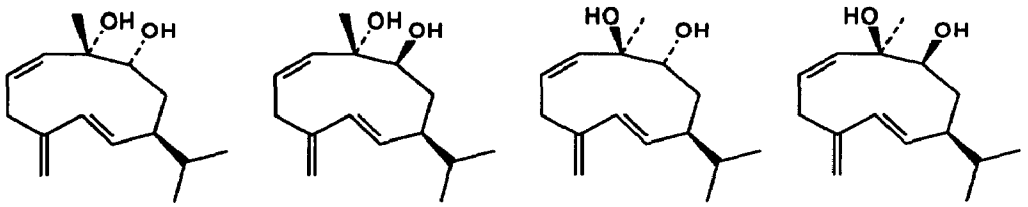
Abstract: We have carried out an enantioselective synthesis of (–)-periplanone C by a route involving titanium-induced, intramolecular pinacol coupling reaction of a 1,10 keto aldehyde as the key step. The coupling occurs with predictable stereochemistry to give a mixture of two diol products in greater than 60% yield.

We have been interested recently in exploring the synthetic utility of the intramolecular pinacol reaction, whereby a cyclic diol is prepared by reductive coupling of a dicarbonyl compound. Although an old and general method of carbon-carbon bond formation,[1] the pinacol coupling reaction has been little used for the synthesis of complex molecules. Our early work on the synthesis of crassin[2,3] was hindered by difficulties in controlling the stereochemistry of the diol products, but we have recently reported a model that makes it possible to predict product stereochemistry with reasonable accuracy.[4] As a test of the model, we decided to undertake a total synthesis of some periplanones.

The periplanones are a group of 10-membered ring sesquiterpenes that act as sex pheromones for the American cockroach *Periplaneta americana*. Since the initial structure determination of periplanone B in 1976,[5] numerous syntheses have been accomplished,[6-11] and several related substances have been found, including periplanones A,[12] C,[13] and D.[13] Our own plan was to aim for the syntheses of both periplanone C (**3**), a key substance from which other members of the class have been prepared, and periplanone D (**4**). Our planned route was to carry out an intramolecular pinacol reaction of keto aldehyde **1** to obtain a predictable mixture of diols **2**, from which **3** and **4** could then be obtained.



Of the four diol products that might result from pinacol coupling of keto aldehyde **1**, MM2 calculations of the corresponding dimethylsilyl acetals predict that cis isomer **2a** will predominate (78%) and that trans isomer **2b** will be formed in a lesser amount (15%). Isomers **2c** and **2d** should form only to a negligible extent (5% and 2%, respectively).[14]



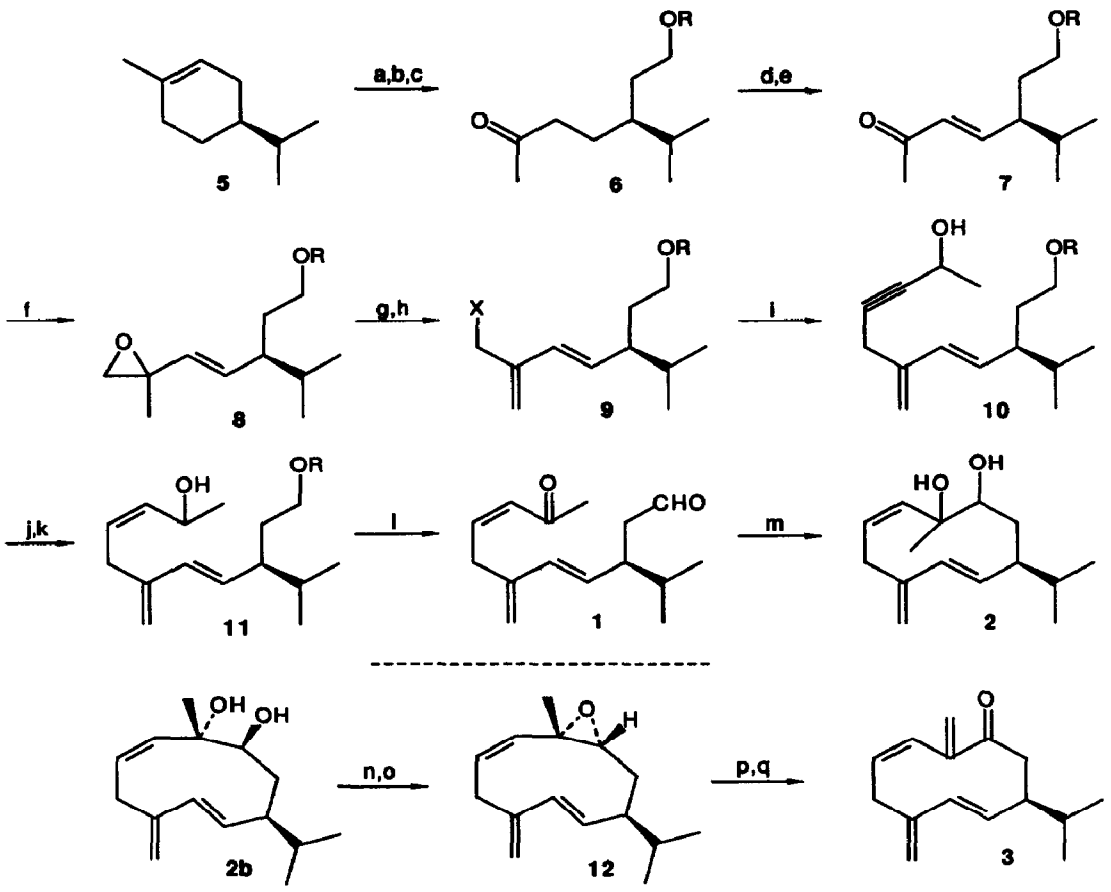
2a (78%) **2b** (15%) **2c** (5%) **2d** (2%)

An enantioselective synthesis of cyclization substrate **1** was accomplished as shown in the scheme. Our starting material was (*S*)-(–)-menthene (**5**), itself prepared from commercially available (*S*)-(–)-limonene by selective reduction over the Wilkinson catalyst. Ozonolysis of **5** gave a keto aldehyde, which was selectively reduced and then protected with *tert*-butyldiphenylsilyl chloride to give keto silyl ether **6**. Bromination followed by dehydrobromination gave enone **7**, and reaction with dimethylsulfonium methylide[15] then gave epoxide **8**. Treatment of **8** with lithium diisopropylamide opened the epoxide ring to produce an allylic alcohol,[16] which was converted into allylic chloride **9** by reaction with methanesulfonyl chloride and LiCl in DMF.[17] Copper-catalyzed acetylide alkylation reaction of **9** with 3-butyn-2-ol gave **10**,[18] reduction over the Lindlar catalyst generated the cis compound (**11**), and deprotection of the silyl ether followed by oxidation with the Dess-Martin periodinane[19] gave keto aldehyde **1**.

Addition of **1** to a slurry of low-valent titanium in dimethoxyethane over a period of 36 h at 0°C gave a mixture of diol products in 60% yield.[20] As predicted, only two diols were formed in substantial amounts. NMR analysis of each let us assign structure **2b** to the major product (62% actual versus 15% predicted) and structure **2a** to the minor product (30% actual versus 78% predicted).[21] Only minor amounts of diols **2c** and **2d** were formed, as expected.

Completion of the periplanone C synthesis was accomplished by treatment of **2b** with methanesulfonyl chloride, followed by exposure of the hydroxy mesylate to tetrabutylammonium hydroxide. The resultant epoxide, **12**, was then opened by reaction with lithium diisopropylamide to give an allylic alcohol, which was oxidized to give periplanone C. The synthetic material was spectroscopically identical to the natural product.[22] The synthesis required 17 steps from (*S*)-(–)-menthene and took place in an overall yield of 4%.

In principle, periplanone D (**4**) could be prepared stereoselectively from either diol **2a** or **2b** by pinacol rearrangement, and in fact it was this possibility that first led us to undertake our work. Unfortunately, treatment of either diol under a variety of acidic conditions led only to a bicyclic intramolecular cyclization product.



Scheme: Synthesis of Periplanone C (a) O_3, ethanol, –78°C; (b) 2 equiv. $NaBH_4$, THF/ethanol; (c) *t*-Bu(Ph)$_2$SiCl, imidazole, DMF, 93% for 3 steps; (d) Br_2, CCl_4; (e) Li_2CO_3, LiBr, DMF, 67%; (f) $(CH_3)_2S{=}CH_2$, THF; (g) LiN(*i*Pr)$_2$, THF, 60% for 2 steps; (h) MsCl, LiCl, DMF; (i) 3-butyn-2-ol, K_2CO_3, CuI, Bu_4NBr, DMF, 75% for 2 steps; (j) H_2, Lindlar, 90%; (k) Bu_4NF, THF, H_2O, 83%; (l) Dess-Martin periodinane, NaOAc, CH_2Cl_2; (m) $TiCl_3{\cdot}DME_{1.5}$, Zn-Cu, DME, 60% for 2 steps; (n) MsCl, ether/pyridine; (o) Bu_4NOH, THF; (p) LiN(*i*Pr)$_2$, THF, 38% for 3 steps; (q) Dess-Martin periodinane, 84%.

This successful completion of the periplanone C synthesis constitutes formal enantioselective syntheses of periplanones D and A since Hauptmann has converted C into D by reduction with potassium tri-*sec*-butyl borohydride[13a] and C into A by oxidation with *tert*-butylhydroperoxide in the presence of potassium hydride.[23] More importantly, however, this work demonstrates the value of the intramolecular pinacol reaction in organic synthesis.

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22. ^{1}H NMR (500 MHz) δ 0.89 (d, J = 6.6 Hz, 3 H), 0.94 (d, J = 6.6 Hz, 3 H), 1.61 (m, 1 H), 2.10 (m, 1 H), 2.59 (dd, J = 6.8, 12.2 Hz, 1 H), 3.02 (t, J = 15.7 Hz, 1 H), 3.41 (br t, J = 15.8 Hz, 1 H), 4.73 (br t, J = 1.7 Hz, 1 H), 4.93 (br d, J = 1.4 Hz, 1 H), 5.48 (s, 1 H), 5.56 (dd, J = 10.5, 16.4 Hz, 1 H), 5.57 (m, 1 H), 5.78 (br t, J = 1.2 Hz, 1 H), 5.81 (d, J = 16.4 Hz, 1 H), 6.22 (d, J = 11.1 Hz, 1 H).^{13}CNMR (100 MHz) δ 20.05, 20.20, 32.32, 34.35, 43.52, 49.83, 112.74, 121.53, 128.61, 129.70, 130.35, 136.36, 145.12, 149.37, 205.51. GC-FTIR 3051, 2966 (s), 2881, 1723 (s), 1628, 1589, 1455, 1382, 1267, 1102, 1000, 884 cm^{-1}. GC-MS (EI, 80 EV) m/z 216, 201, 145, 118, 105, 83. $[\alpha]_D$ (c 0.1, $CHCl_3$) –283°.
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