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(30) Epoxide yields are based on olefin consumed. These reactions are also accompanied by the competing singlet oxygen ene reaction. We have shown that allylic hydroperoxide cannot epoxidize olefins under our reaction conditions. The higher yields obtained in the phosphite ozonide direct addition cases probably indicates that a bimolecular reaction between the ozonide and diazo compound occurs to give the carbonyl oxide. To the extent that this is true there is less opportunity for the competing ene reaction to occur.

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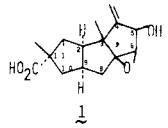
A Stereocontrolled Total Synthesis of (±)-Hirsutic Acid C

Sir:

We report the first fully stereocontrolled synthesis of (±)-hirsutic acid C (**1**), a representative of a novel tricyclic sesquiterpene class whose members possess antibiotic and antitumor activity.[1,2] The key structural problem is the cre-



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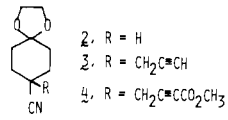
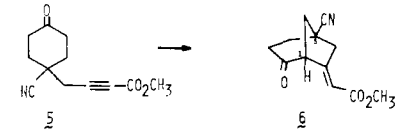


2, R = H
3, R = $CH_2C{\equiv}CH$
4, R = $CH_2C{\equiv}CCO_2CH_3$

ation of four of the seven chiral centers (C(2), C(3), C(9), and C(11)) since it has been shown these four centers allow ultimate control of the remaining three.[2a] Using a rigid bridged bicyclic template, these four centers are introduced with the correct relative stereochemistry and then the polycycle is unraveled to reveal the skeleton of hirsutic acid. Two intramolecular Michael reactions create the key polycycle **13.** Adaptability of this route toward a chiral synthesis is also illustrated.

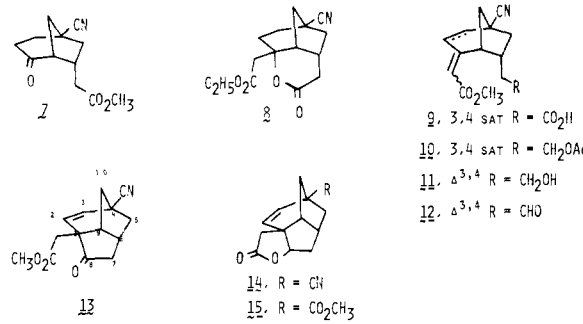
4-Cyanocyclohexanone ketal (**2**) is smoothly alkylated with 1-trimethylsilylpropargyl bromide ($LiN(C_3H_7\text{-}i)_2$, THF, −30 °C) to give after desilylation (KOH, CH_3OH) crystalline cyano ketal **3**,[3] mp 75–76 °C, in 88% yield. Conversion of **3** to the acetylide ion (LDA, TMEDA, THF, −78 °C) must be done with careful maintenance of the low temperature to avoid elimination of cyanide. The acetylide is smoothly carboxylated (CO_2 and then CH_2N_2) to give **4**[3] and the ketal hydrolyzed (PhH, 2.5% aqueous HCl, H_2O, reflux, 6 h) to give cyclohexanone **5**,[3,4] mp 99–101 °C, in 88% yield. While use of acetylenes as Michael acceptors has been rather restricted, they are in fact excellent substrates.[5] Thus, subjection of **5** to triethylamine (4–8 equiv) in refluxing toluene for 12 h gives keto enoate **6**,[3,4] mp 115–116 °C, in 65–70% yield. The stereo-



5 **6**

chemistry of the double bond is proposed as *E* on the basis of the proton at C(1) appearing at δ 3.46, whereas in the very minor *Z* isomer (<5%) this proton appears at δ 4.39—the difference reflecting the additional deshielding by the ester carbonyl group. This reaction establishes the stereochemistry of C(2) and C(11) of hirsutic acid C since C(1) and C(5) of **6** become these carbons in **1.** Hydrogenation (5% $Pd/BaCO_3$, 1 atm, C_2H_5OH-C_2H_5OAc, 80%) of enoate **6** from the exo face establishes the stereochemistry of C(7) in the saturated keto ester **7**,[3] mp 90–92 °C, as shown; this stereochemistry translates into C(9) of hirsutic acid C. Subjecting the keto ester **7** to the Reformatsky reaction ($BrZnCH_2CO_2C_2H_5$, PhH-ether, reflux, 15 min) confirms the stereochemistry of **7** since only the lactone **8**[3] is observed. Subjection of lactone **8** to 0.5 M methanolic sodium methoxide at room temperature for 3 h effects ring opening and transesterification to give acid **9**,[3,4,6] mp 141–146 °C, in 77% overall yield from **7** in which the chemical differentiation of the three functional groups is maintained. Selective reduction of the acid (BH_3-THF, 0 °C, 75%) and acetylation (Ac_2O, pyridine, RT, 89%) generates acetate **10**[3] which is subjected to bromination (NBS, CCl_4, reflux, 30 min), dehydrobromination (LiBr, Li_2CO_3, DMF, 130 °C, 20 min) and hydrolysis (K_2CO_3, CH_3OH, 0 °C, 2 h) without isolating any intermediates to give the dienoate **11**[3,4,6] in 79% yield from enoate **10.** Oxidation of the alcohol **11** to the aldehyde **12**[3] ($C_5H_5N^+HCrO_3Cl^-$, CH_2Cl_2, RT, 60–80%) sets the system up for the second critical Michael reaction.

In situ formation of an acyl anion equivalent for an intramolecular Michael reaction was achieved with 2.3 equiv of 3,4-dimethyl-5-(2′-hydroxyethyl)thiazolium iodide[7] and 50 equiv of triethylamine in refluxing 2-propanol for 5 h to give directly the critical tricyclic ketone **13**,[3,4] mp 118–119 °C, in 67% yield. At this point, the four centers (C(2), C(3), C(9),



7 **8**
9, 3,4 SAT R = CO_2H
10, 3,4 SAT R = CH_2OAc
11, $\Delta^{3,4}$ R = CH_2OH
12, $\Delta^{3,4}$ R = CHO
13
14, R = CN
15, R = CO_2CH_3

and C(11)) of hirsutic acid which correspond to C(9), C(1), C(6), and C(4), respectively, of ketone **13** have been established with correct relative stereochemistry. With the problem of stereochemistry solved, the polycycle must now be unfolded to reveal the hirsutic acid system.

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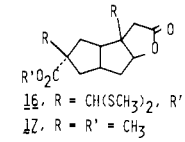
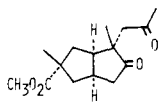
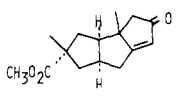
The keto ester was transformed into the lactone **14**,[3,4] mp 158–159.5 °C (K_2CO_3, CH_3OH, H_2O, RT, 2 h; $NaBH_4$, C_2H_5OH, THF, 0 °C, 1 h; Ph_3P, $CH_3O_2CN{=}NCO_2CH_3$, THF, RT, 4 h; overall 92%).[8] The olefinic carbons of the latter, after conversion of the nitrile to the carbomethoxy group (dry HCl, CH_3OH, ether, 96%) were directly converted to methyl groups without isolating any intermediates. Thus, after ozonolysis (CH_3OH, CH_2Cl_2, −78 °C, and then $(CH_3)_2S$), methyl mercaptan and boron trifluoride etherate were added to form the bisthioacetal **16** which was directly subjected to desulfurization with W-5 Raney nickel to give the tricyclic lactone **17**,[3,4] mp 45–47 °C, in 75% yield. The acid **18**[3] (1 N aqueous KOH, THF, reflux, 2 h, and then acidify, 84%, mp 126.5–128 °C) was converted to the known methyl ketone **19**[2a] by standard methods (CH_3Li, THF, −78 °C; CH_2N_2, ether, 0 °C; $C_5H_5NH^+$-CrO_3Cl^-, CH_2Cl_2, NaOAc, RT; 70% yield) and subsequently treated with base (KOC_4H_9-*t*, *t*-C_4H_9OH, RT, 79% yield) to effect an intramolecular aldol reaction to give the known tricycle **20**.[2a] Comparison of its spectral data



16, R = $CH(SCH_3)_2$, R' = CH_3
17, R = R' = CH_3
18, R = CH_3, R' = H



19



20

with those of an authentic sample of **20** confirmed their identity. Furthermore, tricyclic enone **20** was converted to hirsutic acid by the method of Matsumoto et al.[2a] Again, comparison of our synthetic sample of racemic hirsutic acid C with an authentic sample of the natural product by IR, 270-MHz ^1H NMR, ^{13}C NMR, and chromatography confirmed their identity except for optical rotation.[9]

Not only does this route rigorously control relative stereochemistry but it also offers an opportunity to explore control of absolute stereochemistry which is created in the conversion of achiral cyclohexenone **5** to chiral bicyclo[3.2.1]octanone **6**. Treatment of **5** with (−)-quinine gave the bicyclic ketone **6** in 83% yield with $[\alpha]^{25}_D$ −68° (*c* 0.84 acetone). Use of 25 mol % of the chiral shift reagent Eu(hfbc)$_3$[11] separates the methyl ester signals of the two enantiomers (δ 4.17 and 4.21) at 270 MHz to allow determination of the ratio as 65% (−) enantiomer and 35% (+) enantiomer, respectively. This degree of asymmetric induction is delightfully high for a Michael reaction with a carbon nucleophile[10] and offers the promise of a chiral synthesis of this interesting class of compounds.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for their generous support of our programs. We thank Professor G. Mellows for a generous gift of hirsutic acid C and Professor Matsumoto for copies of the spectral data of tricyclic enone **20.** We also express our appreciation to Dr. V. Reutrakul for his early contributions to this project.

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(3) This compound has been fully characterized by spectroscopic means and elemental composition established by elemental analysis and/or high resolution mass spectroscopy.

(4) **5:** IR 2252, 1728, 1715 cm^{-1}; NMR δ 2.78 (2, H, s), 3.76 (3 H, s). **6:** IR 2250, 1716, 1663 cm^{-1}; NMR δ 3.46 (1 H, m), 3.71 (3 H, s), 5.88 (1 H, t, J = 3 Hz). **7:** IR 2247, 1722 cm^{-1}; NMR δ 1.7–3.0 (12 H, m), 3.64 (3 H, s). **9:** IR 2400–3600, 2240, 1718, 1655 cm^{-1}; NMR δ 1.6–3.0 (11 H, m), 3.64 (3 H, s), 4.39 (1 H, t, J = 4 Hz), 5.68 (1 H, s). **11:** IR 3630, 3510, 2242, 1719, 1630, 1603 cm^{-1}; NMR δ 1.1–3.0 (8 H, m), 3.53 (2 H, m), 3.66 (3 H, s), 4.36–4.64 (0.7 H, *m*), 5.48 (0.3 H, s), 5.66 (0.7 H, s), 6.07 (0.7 H, d, J = 9.5 Hz), 6.39 (1 H, d, J = 9.5 Hz), 7.36 (0.3 H, d, J = 9.5 Hz). **13:** IR 2246, 1735 cm^{-1}; NMR δ 1.9–3.2 (10 H, m), 3.60 (3 H, s), 5.10 (1 H, d, J = 9 Hz), 6.20 (1 H, d, J = 9 Hz); ^{13}C NMR δ 214.3, 170.9, 135.1, 126.5, 122.2, 55.5, 51.6, 48.8, 44.9, 42.2, 37.6, 37.5, 37.3, 35.2. **14:** IR 2256, 1775, 1648 cm^{-1}; NMR δ 1.8–3.1 (8 H, m), 2.56 (2 H, s), 4.49 (1 H, d, J = 6 Hz), 5.45 (1 H, d, J = 9.5 Hz), 6.10 (1 H, d, J = 9.5 Hz); ^{13}C NMR δ 174.6, 134.6, 127.6, 122.4, 90.6, 55.2, 49.7, 49.1, 41.4, 40.1, 38.0, 37.5 and 36.6. **17:** IR 1787, 1734 cm^{-1}; NMR δ 1.1–2.9 (8 H, m), 1.19 (3 H, s), 1.28 (3 H, s), 2.39 (s, 2 H), 3.63 (3 H, s), 4.50 (1 H, dd, J = 6, 2 Hz).

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(9) The overall yield of 3.6% to tricyclic enone **20** demonstrates the efficiency of this approach compared with that of the earlier nonstereocontrolled synthesis.

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Stereoselective Energy Transfer Induced by Circularly Polarized Light

Sir:

Generation of optical activity in the absence of added chemical or biochemical chiral agents is a fascinating problem of fundamental importance. Photolysis by circularly polarized light (CPL) has been the most successful approach to date.[1,2] Partial photoresolution,[3] asymmetric destruction,[4] and synthesis[5] initiated by CPL have been reported. All of these experiments relied upon the determination of enantiomeric selectivities generated, often in relatively small amounts, in the products or that remained in the reactants subsequent to photodecomposition. We report here the direct consequences of irradiating with CPL. Intramolecular energy transfer, induced by CPL, showed remarkable stereoselectivity.

Emission spectra of D-tryptophan (D-Trp) and L-tryptophan (L-Trp) excited at 284 nm in methanol by unpolarized and by left and right CPL[6] are shown in Figure 1. No difference was observed in the emission spectra between equal concentrations and optical purities of D-Trp and L-Trp if irradiated by unpolarized light. Irradiation by left CPL, however, resulted in appreciably higher fluorescence efficiency of D-Trp than L-Trp. Irradiation with right CPL produced the same difference between D-Trp and L-Trp in the opposite direction (Figure 1). This observation lends credence to the purities of our samples and the equivalence of left and right CPL in our instrument and substantiates the observed effect. Differences in fluores-

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