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A Regiospecific and Highly Stereoselective Approach to the Synthesis of Linearly Fused Tricyclopentanoids. Intramolecular Diyl Trapping Reactions

Sir:

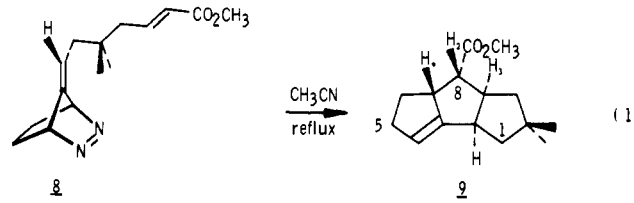
We report herein the first example of an intramolecular 1,3-diyl trapping reaction and the application of the reaction to the construction of the linearly fused tricyclopentanoid skeleton common to a class of naturally occurring sesquiterpenes which possess antibiotic and antitumor activity.[1] The key reaction in our route involves the formation of two new carbon-carbon bonds with simultaneous creation of two of the three five-membered rings in a highly stereoselective process which serves to generate four asymmetric centers with the proper relative stereochemical relationship required for elaboration to the naturally occurring systems.

In the discussion which follows attention will be focused upon (1) the synthesis and trapping of 1,3-diyl **1** (note the relationship of **1** to trimethylenemethane) [The basic synthetic plan involves three important disconnections (labeled A, B, and C) and is illustrated in Scheme I.]; (2) a rationale for the observed high degree of stereoselectivity; and (3) a comparison of inter- and intramolecular diyl trapping reactions for the construction of linearly fused tricyclopentanoids.

The bicyclic azo compound **8**, a convenient source of diyl **1**, was synthesized starting with commercially available 3,3-dimethylglutaric anhydride (**2**) following the route outlined in Scheme II. Successive reduction of **2** with sodium borohydride and diisobutylaluminum hydride (Dibal) afforded the cyclic hemiacetal **3**.[2,3] Wittig condensation of carbomethoxyethylidene triphenylphosphorane with **3**, followed by oxidation of the resulting primary alcohol using the Corey-Suggs procedure, afforded aldehyde **5**.[4,5]

The conversion of **5** into the α,β-unsaturated fulvene **6** proved to be a troublesome task at first, but, after considerable exploration, it was found that uniformly acceptable yields could be obtained using a modification of an approach developed by Freiesleben.[6] Thus, the dropwise addition of a methanolic solution of diethylamine (1.5 equiv) to freshly distilled cyclopentadiene (2.5 equiv) and aldehyde **5** (1.0 equiv) in absolute methanol at 5–10 °C followed by stirring at room temperature for 2 h, recooling to 0–5°C, addition of acetic acid, removal of the methanol, ether extraction, successive washing with 10% sodium bicarbonate and brine, drying ($MgSO_4$), concentration and chromatography over neutral alumina afforded a 91% yield of the desired fulvene: UV λ_{max} (C_2H_5OH) 258 nm (ϵ 20 600). The Diels-Alder reaction of fulvene **6** and di(2,2,2-trichloroethyl) azodicarboxylate proceeded efficiently at 0 °C in ether and was followed immediately by selective monohydrogenation of the endocyclic π bond to form the bicyclic biscarbamate **7** in 70% yield from **6**.[7] Conversion of **7** into the desired azo compound **8** was achieved electrochemically using our recently developed method (note Scheme II).[8,9]

To test the viability of using an intramolecular diyl trapping reaction as a route to linearly fused tricyclopentanoids, azo compound **8** was refluxed in acetonitrile for 6 h. A highly stereoselective reaction ensued and, after chromatographic purification, linearly fused tricyclopentanoid **9** was isolated in 50% overall (nonoptimized) yield from biscarbamate **7**[10,11] (eq 1).



(1)

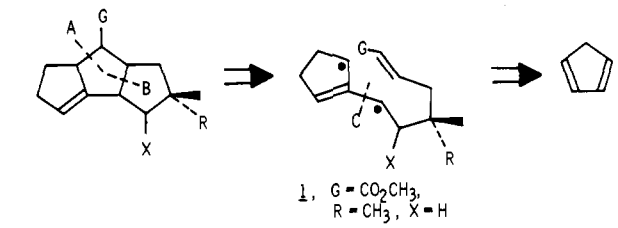
8 **9**

The stereochemical assignment shown in eq 1 follows from ^1H NMR studies. In particular, it was found that the methine hydrogen α to the ester group (H_2, δ 2.58) was split into a clean doublet with J = 8 Hz thereby implying a 0-Hz coupling between H_2 and one of the bridgehead protons. Molecular models reveal that, of the four possible linearly fused tricyclopentanoids which could have been formed, only **9** has a dihedral angle of 90° between H_2 and H_3. Europium shift reagent experiments corroborate the assignment.

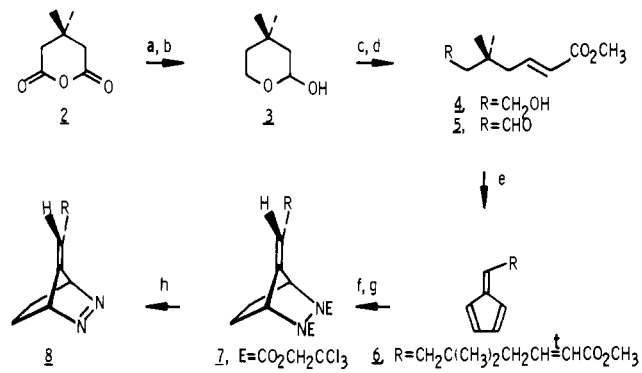
The observed high degree of stereoselectivity can be rationalized by noting that there exist bonding secondary orbital interactions between C_A and C_B of the diyl and the carbonyl carbon of the unsaturated ester unit (note Scheme III).[12] To the extent that these interactions lower the transition state energy of the path leading to **9** relative to the other possible linearly fused tricyclopentanoids, one would predict its preferential formation.

We recently reported that linearly fused tricyclopentanoids can be synthesized using an intermolecular diyl trapping reaction.[13] Of the two methods (inter- vs. intra-), the intramo-

Scheme I

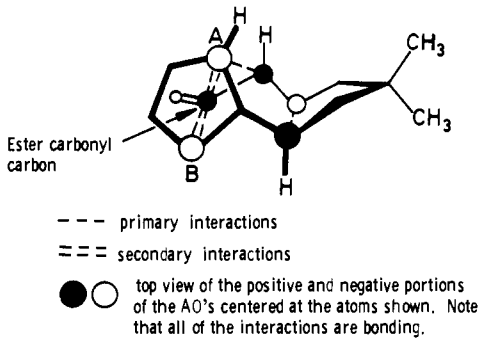


Scheme II[a]



[a] (a) $NaBH_4$, THF, 0 °C and then raise to room temperature, 74%; (b) Dibal, ether, −20 °C and then raise to room temperature, 74%; (c) $Ph_3P{=}CHCO_2CH_3$, benzene, reflux, 40%;[14] (d) $C_5H_5N^+HCrO_3Cl^-$ (PCC), CH_2Cl_2, room temperature, 92%; (e) 2.5 equiv of cyclopentadiene, 1.5 equiv of Et_2NH, 1.0 equiv of aldehyde **5**, absolute methanol, 5–10 °C and then warm to room temperature, 91%; (f) $Cl_3CCH_2O_2CN{=}NCO_2CH_2CCl_3$, ether, 0 °C, and then (g) H_2, 10% Pd/C, $CHCl_3$/EtOAc, atmospheric pressure, room temperature, 70% from **6**; (h) e^- (1.75 V vs. a silver/silver chloride reference electrode), DMF, 0.1 N $LiClO_4$, room temperature followed by cooling to 0 °C, and the addition of 3.0 equiv of $K_3Fe(CN)_6$.

Scheme III



lecular approach is superior for the following reasons. (1) Excess diylophile is required in the intermolecular route to avoid side reactions. While it is generally easy to recover the diylophile, distillation and/or chromatography is required; with the intramolecular approach, the diylophile is built in, thereby obviating removal of excess diylophile. (2) The intermolecular trap leads to a mixture of stereoisomers whereas the intramolecular trap is highly stereoselective. (3) The intermolecular trap affords a mixture of regioisomers whereas the intramolecular trap is regiospecific. For example, an examination of diyl **1** reveals that the groups X, G, and the A-ring π bond can assume only one regioisomeric relationship upon closure to a tricyclopentanoid. This result is of use in regard to the synthesis of the coriolins and the antitumor agent diketocoriolin B.

We believe that the intramolecular 1,3-diyl trapping reaction represents a general and useful route to linearly fused tricyclopentanoids. We are presently exploring the conversion of **9** into (±)-hirsutene as well as the use of the intramolecular 1,3-diyl trapping reaction for the synthesis of the coriolins.

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(5) Satisfactory IR, ^{1}H NMR, elemental analyses, and/or high resolution mass spectra have been obtained. The complete spectral data will be reported in our full paper.
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(7) The selection of di(2,2,2-trichloroethyl) azodicarboxylate rather than dimethyl or diethyl azodicarboxylate for the Diels–Alder reaction allowed selective operation on the carbamate esters without concern for possible side reactions involving the α,β-unsaturated ester group.
(8) Little, R. D.; Carroll, G. L. *J. Org. Chem.*, scheduled for publication.
(9) Azo compound **8**: ^{1}H NMR ($CDCl_3$–Me_4Si) δ 7.01 (dt, 1 H, J = 8, 16 Hz, β-vinyl), 5.87 (dt, 1 H, J = 1, 16 Hz, α-vinyl), 5.40 and 5.17 (two br s, 1 H each, bridgeheads), 5.20 (t, 1 H, J = 8 Hz, C_7=C*H*R), 3.78 (s, 3 H, CO_2CH_3), 2.05 (dd, 2 H, J = 1, 8 Hz, CH_2CH=$CHCO_2CH_3$), 1.90 (d, 2 H, J = 8 Hz, $CH_2C(CH_3)_2$), 1.2 (m, 4 H, RCH_2CH_2R), 0.92 (s, 6 H, $(CH_3)_2C$).
(10) There is a minor, but as yet uncharacterized product which is formed.
(11) Linearly fused tricyclopentanoid **9**: IR (film) 3050, 2950, 1735, 1385, 1370, and 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$–Me_4Si) δ 5.2 (overlapping dt, 1 H, J = 2, 3 Hz, vinyl), 3.61 (s, 3 H, CO_2CH_3), 2.58 (d, 1 H, J = 8 Hz, $CHCO_2CH_3$), 1.03 (s, 3 H, CH_3), 0.92 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, note structure **9** for the numbering system used) 26.7, 25.9 and 28.2 (*gem*-CH_3 groups), 37.0, 39.9, 40.9 (C_{11}), 47.3, 47.6, 50.5, 50.7, 51.4 (CO_2CH_3), 51.6, 117.5 (C_4), 154.5 (C_3), 175.1 (CO_2CH_3).
(12) The secondary orbital interaction argument presumes that the degenerate pair of diyl NBMO's are perturbed so that the symmetric combination is the HOMO and the antisymmetric combination is the LUMO. For an analogous ordering of MO's see Siemionko, R.; Shaw, A.; O'Connell, G.; Little, R. D.; Carpenter, B. K.; Shen, L.; Berson, J. A. *Tetrahedron Lett.* **1978**, 3529–3532.
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(14) The reported yields are not optimized.

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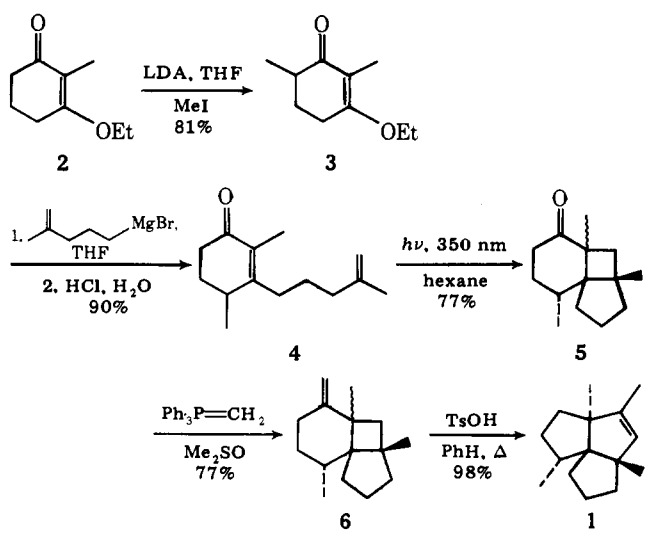
Total Synthesis of (±)-Isocomene

Sir:

The tricyclic sesquiterpene isocomene (**1**) was isolated in 1977 by Zalkow and co-workers[1] from rayless goldenrod (*Isocoma wrightii*), a plant notorious for its toxicity to cattle and sheep. Although compound **1** did not turn out to be the toxic constituent of the plant, its novel structure embodies an almost unique structural feature—three contiguous quaternary chiral centers—and constitutes a significant challenge to synthesis. In this communication we report the total synthesis of isocomene by an efficient route involving an intramolecular [2 + 2] photocycloaddition as the key bond-forming reaction (Scheme I). Though [2 + 2] cycloadditions are well known in synthesis, only recently has the intramolecular version been applied to a natural product.[2]

Enol ether **2**, readily available from dihydroresorcinol,[3] is methylated by the procedure of Stork and Danheiser[4] to obtain **3** (81%). This material reacts with the Grignard reagent prepared from 5-bromo-2-methyl-1-pentene[5] to afford an unstable alcohol which is treated with 5% aqueous HCl at 25 °C for 2 h to obtain dienone **4** (UV (hexane) λ_{max} 240 nm (log ϵ 4.14), 324 (1.52)) in 90% yield after simple chromatographic purification and bulb-to-bulb distillation. Irradiation of dienone **4** as a 10^{-2} M hexane solution with a Rayonet reactor using 350-nm lamps results in the formation of cycloadduct **5** (^{1}H NMR ($CDCl_3$) 0.83 (3 H, d, J = 7 Hz), 1.00 (3 H, s), 1.10 (3 H, s); IR (neat) 1705 cm^{-1}; UV (hexane) λ_{max} 283 nm (log

Scheme I



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