Tetrahedron Letters No. 4, pp 305 - 308.

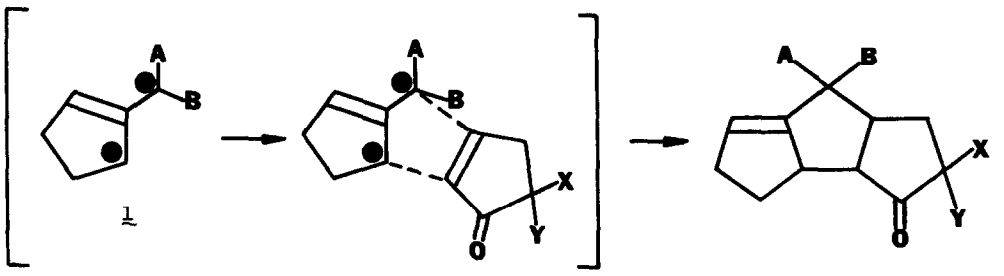
0040-4039/79/0122-0305$02.00/0

A NEW ROUTE TO LINEARLY FUSED TRICYCLOPENTANOIDS. DIYL TRAPPING REACTIONS IN ORGANIC SYNTHESIS.

R. Daniel Little,* Ahmed Bukhari, and Manuel G. Venegas
Department of Chemistry, University of California, Santa Barbara, CA 93106

The current interest in linearly fused tricyclopentanoid carbon skeletons as exemplified by hirsutic acid,[1] hirsutene,[2] the coriolins and diketocoriolin B,[3] and capnellane,[4] has led to the development of several synthetic routes to these systems. Thus far, the most successful and general of these routes is based upon the idea of successively annelating two cyclopentane rings onto a preformed cyclopentane or annelation of the last ring onto a preformed bicyclo(3.3.0)octane skeleton.[1c,d,2a] Some of the other useful routes include those based upon: (1) biogenic-like transformations of protoilludenes;[2b,c] (2) intramolecular photochemical[2+2]cycloaddition of a dicylopent-1-enylmethane followed by nucleophilic ring opening of the intermediate bicyclo(2.1.0)pentane system;[5] (3) an oxadi-π-methane photochemical rearrangement of a tricyclo[5.2.2.0^{2,6}]undeca-3,10-dien-9-one ring system followed by hydrogenolysis;[6] and (4) acid catalyzed ring closure of 1,1'-dicyclopentenyl ketone.[7]

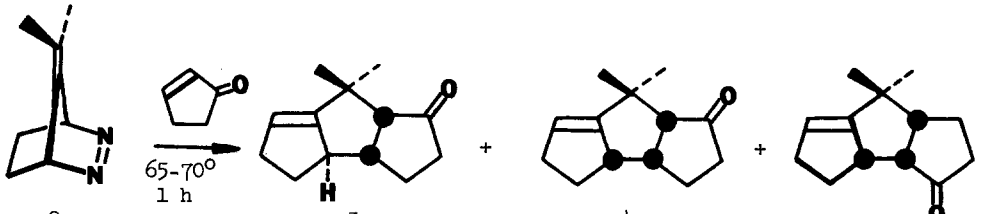
We would like to report a new route to these systems based upon the trapping of a 1,3-diyl related to trimethylenemethane[8] e.g., 1, with cyclopentenone or a substituted cyclopentenone as illustrated below. This route allows the facile construction of the tricyclopentanoid skeleton from two simple precursors which, when appropriately functionalized (i.e., A, B, X and Y), provide entries to the substituent patterns found in naturally occuring systems.



The trapping reaction is typically run for approximately 1 h at 65-70° in the presence of a large excess of diyl trapping agent. When the reaction is complete, the excess trapping agent is recovered for reuse using distillation and/or a combination of distillation and chromatography. Thus, despite the fact that a large excess of trapping agent is required in order to obviate diyl dimerization and favor formation of fused rather than bridged cycloadducts, the unused material is easily recovered.

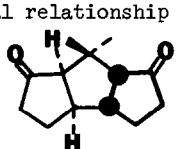
In a typical example, heating the bicyclic azo compound 2 in the presence of cyclopentenone (65-70°, 1 h, 10 eq. enone) afforded the isomeric tricyclopentanoids 3-5 in isolated yields of 90-98% (3/4/5 = 1.3/1/3). The products were isolated using medium pressure liquid chromatography (mplc; EM reagents silica gel 60, 230-400 mesh ASTM, 15% Et_2O in hexane); 3, ir (film)

1732 cm^{-1}; nmr (^1H, $CDCl_3$) δ 5.20 (X portion of an ABX pattern, 1 H, $J_{AX} + J_{BX}$ = 7.2 Hz, vinyl), 2.73-3.3 (br m, 1 H), 1.4-2.7 (m, 10 H), 1.30 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3); m.s. 190 (M^+), 175 (M-CH_3), 162 (M-CO), 147 (M-CO-CH_3), 133 (M-CO-CH_3-CH_2), 119 (M-CH_2CH_2CO-CH_3), 108 (base peak, M-cyclopentenone); 4 ir ($CHCl_3$) 1732 cm^{-1}; nmr (^1H, $CDCl_3$), δ 5.29 (X of an ABX, 1 H, $J_{AX} + J_{BX}$ = 7.8 Hz, vinyl), 3.13-3.76 (br m, 1 H), 1.3-3.0 (m, 10 H), 1.19 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3); m.s. 190 (M^+); 175 (M-CH_3), 162 (M-CO), 147 (M-CO-CH_3), 119 (M-CH_2CH_2CO-CH_3), 108 (base peak, M-cyclopentenone), 5, ir (film) 1735 cm^{-1}; nmr (^1H, $CDCl_3$) δ 5.37 (X of an ABX, 1 H, $J_{AX} + J_{BX}$ = 7.8 Hz, vinyl), 3.0-3.7 (br m, 1 H), 1.2-3.0 (M, 10 H), 1.13 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3); m.s. 190 (M^+), 175 (M-CH_3), 109 (M-CH_2CH_2CO-CH_3), 108 (base peak, M-cyclopentenone). We were unable to isolate the cis, anti isomer of 5; no doubt it is probably formed but is present in only small amounts.



2 3 4 5

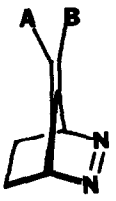
The product regiochemistry was determined from PMR shift reagent experiments using $Eu(fod)_3$. In particular the progressive addition of $Eu(fod)_3$ afforded a much larger change in the methyl group resonances for the regioproximal (carbonyl and methyls) isomers 3 and 4 than for the regiodistal isomer 5. The stereochemical assignments are based upon a combination of chemical and spectroscopic experiments. For example, isomer 3 was converted to diketone 6 using the sequence: B_2H_6, THF, 0° → R.T.; ^-OH, H_2O_2; $H_2Cr_2O_7$, Et_2O/H_2O. ^1H and ^{13}C nmr clearly show that the methyl groups of 6 are magnetically equivalent--as required for a compound possessing a C_2 symmetry axis (i.e., cis, anti, cis-stereochemistry); 6, ir (film) 1730 cm^{-1}; nmr (^1H, $CDCl_3$) δ 1.2 (s, 6 H, 2 CH_3), 1.4-3.2 (m, 12 H); ^{13}C (ref. to $CDCl_3$) 27.5 CH_3 groups; m.s. 206 (M^+, parent), 191 (M-CH_3), 178 (M-CO), 163 (M-CH_3-CO), 150 (M-2 CO), 149 (M-CH_3-CH_2CO), 135 (M-CH_3-CH_2CO-CH_2), 134 (M-cyclopentenone), 121(M-CH_3-CH_2CO-2 CH_2), 79 (m/e 121-ketene). Therefore, 3 and 4 possess the stereochemical relationship shown. It has thus far been more difficult

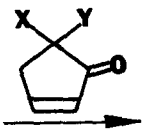


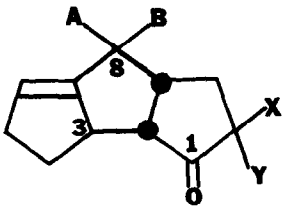
6

to unambiguously establish the stereochemistry of the major isomer 5; we tentatively assign the cis, syn relationship.

In addition to the trapping experiment discussed above, we have performed several others as summarized in the equation illustrated below. At the present time, we do not clearly understand why the yield drops so dramatically when 5-methyl-5-carboethoxycyclopentenone is used in place of cyclopentenone though we speculate that steric factors may be responsible. We also suggest that the reason for the lower yield when the p-methoxyphenylazo compound 8







2, A=B=CH_3

8, A=H, B=p-$CH_3OC_6H_5$

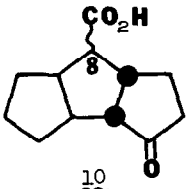
3,4,5, A=B=CH_3; X=Y=H; 90-98%

7, A=B=CH_3; X=CH_3, Y=$CO_2C_2H_5$; 50%

9, A=H, B=p-$CH_3OC_6H_4$; X=Y=H; 24-30%

is used may be due to an electronic perturbation caused by the p-methoxy group in a fashion similar to that which has recently been discussed in relation to the dimethoxy azo compound (A=B=OCH_3).[9] Despite the lower yields for 7 and 9, the reaction still provides a simple entry to a reasonably complex ring system.

The p-$CH_3OC_6H_4$ group of 9 was deliberately chosen to allow functionalization of the tricyclopentanoid at C_8. This was accomplished by hydrogenation at atmospheric pressure (H_2, Pd/C, EtOAc) and ozonolysis (O_3, CH_2Cl_2, 0^o; Jones oxidation) to afford 10. The reason for choosing p-$CH_3OC_6H_4$ rather than a more conventional carbonyl synthon will be discussed in future publications.



10

Finally, we are presently exploring other examples of this reaction and we are focusing particular attention upon (1) increasing regio and stereochemical control; (2) structural modification of the tricyclopentanoids produced; and (3) other methods of functionalizing C_8.

Acknowledgment. We are grateful to the Public Health Service (Grant No. CA21144-01), the Cancer Research Coordinating Committee of the University of California, and the UCSB Committee on Research for support of this research. A.B. would like to thank the University of Petroleum and Minerals, Dhahran, Saudi Arabia, for a fellowship; M.V. thanks the University of California for a fellowship.

1. (a) G. Mellows, P. G. Mantle, T. C. Feline and D. J. Williams, Phytochemistry, 12, 2717 (1973); (b) T. C. Feline, G. Mellows, R. B. Jones and L. Phillips, J.C.S., Chem. Comm., 63 (1974); (c) H. Hashimoto, K. Tsuzuki, F. Sakan, H. Shirahama and T. Matsumoto, Tetrahedron Lett., 3745 (1974) (d) P. T. Lansbury, N. Y. Wang and J. E. Rhodes, ibid., 2053 (1972) and refs. therein.

2. (a) S. Nozoe, J. Furukawa, U. Sankawa and S. Shibata, ibid., 195 (1976); (b) Y. Ohfune, H. Shirahama and T. Matsumoto, ibid., 2795 (1976); (c) K. Hayano, Y. Ohfune, H. Shirahama and T. Matsumoto, ibid., 1991 (1978).

3. (a) S. Takahashi, H. Naganawa, H. Iinuma, T. Takita, K. Maeda and H. Umezawa, ibid., 1955 (1971); (b) M. Tanabe, K. Suzuki and W. C. Jankowski, ibid., 2271 (1974); (c) T. Takeuchi, S. Takahashi, H. Iinuma and H. Umezawa, J. Antibiotics, 24, 631 (1971); (d) N. Nakamura, T. Takita, H. Umezawa, M. Kunishima, Y. Nakayama, Y. I. Iitaka, ibid., 27, 301 (1974);

(e) M. Ishizuka, H. Iinuma, T. Takeuchi and H. Umezawa, ibid., 25, 230 (1972); (f) T. Kunimoto and H. Umezawa, Biochimica et Biophysica Acta, 318, 78 (1973).

4. (a) M. Kaisin, Y. M. Sheikh, L. J. Durham, C. Djerassi, B. Tursch, D. Daloze, J. C. Braekman, D. Losman and R. Karlsson, Tetrahedron Lett., 2239 (1974); (b) E. Ayanoglu, T. Gebreyesus, C. M. Beechan, C. Djerassi and M. Kaisin, ibid., 1671 (1978).

5. J. S. H. Kueh, M. Mellor and G. Pattenden, J.C.S., Chem. Comm., 5 (1978).

6. K-I. Hirao, S. Unno and H. Miura, Chem. Pharm. Bull., 25 (12), 3354 (1977).

7. P. E. Eaton, C. Giordano, G. Schloemer and U. Vogel, J. Org. Chem., 41, 2238 (1976).

8. See inter alia (a) J. A. Berson, C. D. Duncan and L. R. Corwin, J. Amer. Chem. Soc., 96, 6175 (1976); (b) J. A. Berson, L. R. Corwin and J. H. Davis, ibid., 96, 6177 (1976); (c) J. A. Berson, C. D. Duncan, G. O'Connell and M. S. Platz, ibid., 98, 2358 (1976).

9. R. Siemienko, A. Shaw, G. O'Connell, R. D. Little, B. K. Carpenter, L. Shen and J. A. Berson, Tetrahedron Lett., 3529 (1978).

(Received in USA 22 September 1978)