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A NEW APPROACH TO THE SYNTHESIS OF A BICYCLO[5.3.0]DECANE SYSTEM FROM 7-ACETOXYTRICYCLO[5.3.0.0^{1,5}]DECAN-2-ONES THROUGH RETRO- AND RE-ALDOLIZATION FOLLOWED BY GROB FRAGMENTATION

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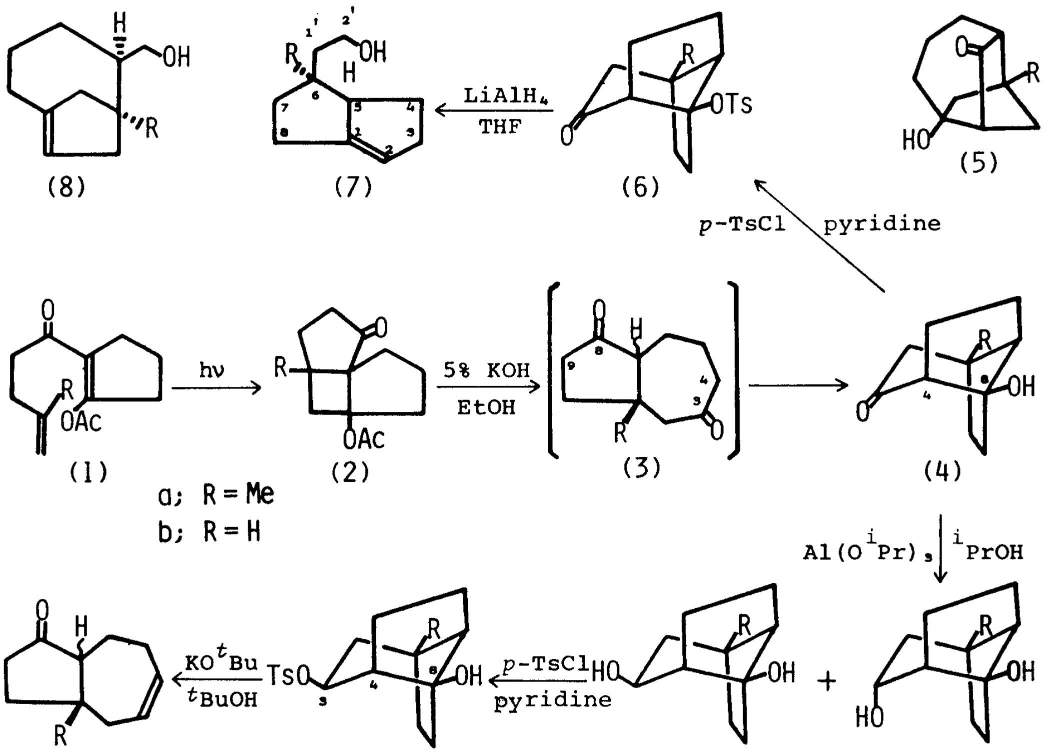
Described here is a novel and simple route to the unsaturated hydroazulenones, bicyclo[5.3.0]dec-3-en-8-ones (12a,b), from photoproducts, 7-acetoxytricyclo[5.3.0.0^{1,5}]decan-2-ones (2a,b).

KEYWORDS —— aldolization; Grob fragmentation; tricyclo[5.3.0.0^{1,5}]decane; tricyclo[5.3.0.0^{4,8}]decane; bicyclo[5.3.0]decane

Much effort has been directed to the total synthesis of the natural terpenoids possessing a bicyclo[5.3.0]decane system (hydroazulene skeleton) because of their peculiar structures and varied biological activities.[3)] In this connection, we recently reported[4)] a new and efficient intramolecular [2+2] photocycloaddition of 1-acetoxy-2-(pent-4-enoyl)cyclopentenes (1a,b) leading to 7-acetoxytricyclo[5.3.0.0^{1,5}]decan-2-ones (2a,b). We now report the synthesis of new hydroazulenes, bicyclo[5.3.0]dec-3-en-8-ones (12a,b), which were suitably functionalized at the positions necessary for elaboration of guaiane and pseudoguaiane type sesquiterpenoids and for further transformation to dolastane type diterpenoids with a linear 6-7-5 ring system, some of which show interesting pharmacological activities.[3b)]

The tricyclodecanones (2a,b) as starting materials were readily obtained as described previously.[4)] It is well-documented that the hydrolysis of 1-acetoxy-2-acylcyclobutanes readily causes the ring opening on concurrent retro-aldolization yielding 1,5-diones.[5)] However, we found that treatment of (2a) with 5% ethanolic potassium hydroxide at r.t. for 2 h directly gave the ketol, 8-hydroxy-1-methyltricyclo[5.3.0.0^{4,8}]decan-3-one (4a)[2)] [colorless prisms, mp 103-104°C, $\nu_{max}(CHCl_3)$: 3580, 3370(br), 1705 cm^{-1}; ^{13}C-NMR($CDCl_3$)δ: 24.4(q), 21.2, 28.0, 31.6, 38.1, 48.0(each t), 57.2, 63.7(each d), 43.3, 89.1, 212.2(each s)] as a sole product in 97.6% yield instead of the literally expected 1-methylbicyclo[5.3.0]-decane-3,8-dione (3a).[6)] It is obvious that the ketol (4a) resulted from the C_4 to C_8 aldol condensation of the dione (3a). The ketol of alternative structure (5a) resulting from the C_9 to C_3 condensation was not detected.

In order to support the structural assignment depicted by (4a), the following chemical transformation was performed. Tosylation of (4a) with 3.0 eq of *p*-toluenesulfonyl chloride in pyridine at r.t. for *ca.* 5 days gave the tosylate (6a) [colorless needles, mp 108-110°C, 96%], which, after treatment with an excess of lithium aluminium hydride in tetrahydrofuran at r.t., gave an alcohol [a colorless oil, 92.8%] as a result of reductive fragmentation[7] of β-tosyloxy ketone moiety in (6a). Its structure was best represented by the formula (7a). In the 400 MHz ^{1}H-NMR spectrum of (7a),[8] the ABX_2 type signals due to hydroxymethylene protons were observed at 3.68 and 3.71 ppm, that evidently ruled out the structure (8a) resulting from the alternative ketol (5a). Furthermore, all the NMR signal assignments on the basis of the structure (7a) was corroborated by double resonance experiments.



(8) (7) (6) (5) (1) (2) (3) (4) (12) (11) (9) (10)

The conversion of 8-hydroxy-1-methyltricyclo[5.3.0.0^{4,8}]decan-3-one (4a) to the 1-methylbicyclo[5.3.0]decane system, including the cleavage of the C_4-C_8 bond, was performed as follows. It was necessary to control stereochemically the reduction of the carbonyl function in (4a) so as to give the equatorial alcohol (9a). This is because the C_4-C_8 bond cleavage through Grob fragmentation[9] on the diol monotosylate (11a) requires the specific configuration in which the tosyloxy function as the leaving group is oriented antiperiplaner to the C_4-C_8 bond. In comparison with all the other reduction methods ($NaBH_4$, $LiAlH_4$, Raney-Ni, Li/liq. NH_3) attempted so far,[10] Meerwein-Ponndorf-Verley reduction was the best for this purpose. Namely, treatment of (4a) with 3.0 eq of aluminium triisopropoxide in refluxing isopropyl alcohol for *ca.* 7 days[11] afforded the diols (9a)[12] [colorless granules, mp 127.5-129°C] and (10a)[12] [colorless needles, mp 128.5-129°C] in a 95:5 ratio in 91.0% gross yield. Tosylation of (9a) with 1.3 eq of *p*-toluenesulfonyl chloride in pyridine at r.t. overnight gave the monotosylate (11a) [colorless needles, mp 94-95 °C] in 92.5% yield. Finally, (11a) was subjected to the Grob fragmentation using 3.0 eq of potassium *tert*-butoxide in *tert*-butyl alcohol at 40 °C for 1 h to furnish the target compound, 1-methylbicyclo[5.3.0]dec-3-en-8-one (12a), in 88.2% yield as a 3:2 C_7-epimeric mixture which was separated by HPLC (Nucleosil 50-5, hexane:ethyl acetate=30:1) into pure epimers.[13]

The gross structure of the major epimer of (12a) [a colorless oil as early eluent from HPLC] was determined on the basis of its high resolution mass spectrum [Found: m/e 164.1192, Calcd for $C_{11}H_{16}O$: m/e 164.1202], infrared absorbtion band [$\nu_{max}(CCl_4)$: 1740 cm^{-1} (characteristic for cyclopentanone function)], and ^1H- and ^{13}C-NMR spectra.[14a] The assignment of proton signals in the ^1H-NMR spectrum (400 MHz) was concordant with the results of detailed spin decoupling and deuterium exchange[15] experiments. The stereochemistry of the ring juncture of this compound was assigned to be *cis* on the following evidence; the broad double doublet signal at 1.87 ppm due to C_2-βH was sharpened by irradiation at 2.07 ppm (C_7-H signal) or by deuteration of C_7-H,[15] indicating a W path long-range coupling (J=*ca*. 0.5 Hz) between C_2-βH and C_7-H. This result revealed that C_2-βH and C_7-H are in a pseudo 1,3-diequatorial relationship that is compatible only with the *cis* epimer of (12a). The *cis* ring juncture was also supported by the observation of NOE enhancement (12%) between C_7-H and the methyl protons. Therefore, we assigned the major epimer to be *cis*-(12a) and the minor epimer to be *trans*-(12a)[14b] [a colorless oil, $\nu_{max}(CCl_4)$: 1743 cm^{-1}].

On the other hand, 7-acetoxytricyclo[5.3.0.0^{1,5}]decan-2-one (2b) was successively treated under similar reaction conditions as (2a) to yield (4b)[6] [colorless needles, mp 132-133 °C], (9b) [colorless needles, mp 143-145.5 °C], (11b) [a colorless oil], and final product, bicyclo[5.3.0]dec-3-en-8-one (12b), in 64.4% overall yield [*cis*:*trans*=1:7.5. *cis*-(12b)[16]: a colorless oil, $\nu_{max}(CCl_4)$: 1738 cm^{-1}; ^1H-NMR($CDCl_3$)δ: 5.59-5.67(2H, m). *trans*-(12b)[16]: a colorless oil, $\nu_{max}(CCl_4)$: 1743 cm^{-1}; ^1H-NMR($CDCl_3$)δ: 5.71-5.88(2H, m)].

Further extension of this novel pathway toward the synthesis of natural products is now in progress.

REFERENCES AND NOTES

1) Undergraduate of Science University of Tokyo (1982).
2) All new compounds gave satisfactory spectral properties(IR, ^1H- and ^{13}C-NMR, and MS), and all oily compounds gave satisfactory high mass data and the crystalline compounds afforded acceptable combustion data. All melting points are uncorrected.
3) a) N.H. Fischer, E.J. Olivier, and H.D. Fischer, Progress in the Chemistry of Organic Natural Products, 38, 47 (1979); E. Rodriguez, C.H.N. Towers, and J.C. Mitchell, Phytochemistry, 15, 1573 (1976); b) P. Crews, T.E. Klein, E.R. Hogue, and B.L. Myers, J. Org. Chem., 47, 811 (1982), and references cited therein.
4) H. Seto, Y. Fujimoto, H. Yoshioka, and T. Tatsuno, Chem. Pharm. Bull., 32, 3751 (1984).
5) For a recent review, see W. Oppolzer, Acc. Chem. Res., 15, 135 (1982).
6) Recently, Pattenden *et al*. reported that treatment of (2b) with 5% ethanolic potassium hydroxide at 0 °C gave bicyclo[5.3.0]decan-1,6-dione (3b); see M.J. Begley, M. Mellor, and G. Pattenden, J. Chem. Soc., Perkin Trans. 1, 1983, 1905. However, we obtained the ketol (4b) as the major product and the dione (3b) as the minor product under similar reaction conditions although the

product ratio was somewhat dependent on temperature [°C, (4b):(3b); 25, 90:10; -20, 95:5. (4b): ν_{max}($CHCl_3$): 3610, 3420(br), 1700 cm^{-1}; ^{13}C-NMR($CDCl_3$)δ: 22.8, 28.0, 30.5, 32.0, 41.6(each t), 38.8, 51.4, 64.8(each d), 89.2, 212.9 (each s). (3b): a colorless oil, ν_{max}($CHCl_3$): 1733, 1690 cm^{-1}; ^{13}C-NMR($CDCl_3$)δ : 24.1, 28.1, 29.7, 37.5, 44.1, 48.8(each t), 38.8, 57.1(each d), 211.7, 217.7 (each s)].

7) For the reductive fragmentation of β-tosyloxy ketones, see W. Kraus and C. Chassin, Tetrahedron Lett., 1970, 1003.

8) ^{1}H-NMR($CDCl_3$)δ: 1.03(3H, s, $-CH_3$), 1.36(1H, d/t/d, *J*=14, 7.5, 1 Hz, $C_{1'}$-H), 1.42(1H, d/t, *J*= 14, 7.5 Hz, $C_{1'}$-H), 1.48(1H, d/q, *J*=12.5, 9.5 Hz, C_4-βH), 1.65(1H, d/t/d, *J*=13, 9, 1 Hz, C_7-αH), 1.77(1H, d/t/d, *J*=12.5, 8, 1.5 Hz, C_4-αH), 1.83(1H, br s, -OH), 1.91(1H, d/d/d, *J*=13, 7.5, 3 Hz, C_7-βH), 2.02-2.23(2H, m, C_8-H_2), 2.43-2.64(2H, m, C_3-H_2), 2.69(1H, m, C_5-H), 3.68(1H, d/t, *J*=12.5, 7.5 Hz, $C_{2'}$-H), 3.71(1H, d/t, *J*=12.5, 7.5 Hz, $C_{2'}$-H), 5.22(1H, d/m, *J*=2 Hz, C_2-H).

9) C.A. Grob and P.W. Schiess, Angew. Chem., Int. Ed. Engl., 6, 1 (1967); C.A. Grob, *ibid.*, 8, 535 (1969).

10) Reduction of (4a) by the reagents described above, except Li/liq. NH_3 [(9a):(10a)=7:3], afforded the axial alcohol (10a) as major product [(9a):(10a)=10:90 -1:99].

11) The reduction of the carbonyl function being finished within a day, a consecutive increase of (9a) against (10a) was observed for a week.

12) ^{1}H-NMR($CDCl_3$) spectra of these compounds were reasonable for the assigned configurations on the basis of the peak width at half height of the C_3-H multiplet [(9a):δ 3.91(1H, m, $W_{1/2}$h=20 Hz). (10a):δ 3.87(1H, m, $W_{1/2}$h=11.5 Hz)], and only (9a) underwent Grob fragmentation.

13) Pure epimers separated by HPLC were equilibrated with each other on base treatment [KO^{t}Bu, ^{t}BuOH].

14) a) ^{1}H-NMR($CDCl_3$)δ: 1.21(3H, d, *J*=0.5 Hz, $-CH_3$), 1.71(1H, d/d/d/d, *J*=14.5, 10.5, 4.5, 3 Hz, C_6-H), 1.72(1H, d/t, *J*=13, 9.5 Hz, C_{10}-H), 1.81(1H, d/t, *J*=13, 6.5 Hz, C_{10}-H), 1.87(1H, d/br d, *J*=15, 7.5 Hz, C_2-βH), 1.97(1H, d/d/d/d, *J*=14.5, 8, 6.5, 3 Hz, C_6-H), 2.03(1H, m, C_5-H), 2.07(1H, d/br d, *J*=6.5, 4.5 Hz, C_7-H), 2.14-2.24(1H, m, C_5-H), 2.31(1H, d/d/d, *J*=13.5, 9.5, 6.5 Hz, C_9-H), 2.34(1H, d/d/d, *J*=13.5, 9.5, 6.5 Hz, C_9-H), 2.38(1H, d/d/m, *J*=15, 5 Hz, C_2-αH), 5.59(1H, d/d/d/d, *J*=11, 7.5, 5, 2 Hz, C_3-H), 5.72(1H, d/d/d/d, *J*=11, 6, 5, 2 Hz, C_4-H). ^{13}C-NMR($CDCl_3$)δ: 27.4(q), 23.2, 26.0, 36.1, 36.2, 36.6(each t), 60.1, 127.6, 132.2(each d), 42.3, 220.8(each s).
b) ^{1}H-NMR($CDCl_3$)δ: 0.80(3H, br s, $-CH_3$), 1.16(1H, m, C_6-H), 1.70(1H, d/d/d/d, *J*=12.5, 11, 10, 1 Hz, C_{10}-αH), 1.82(1H, d/d/d, *J*=12.5, 8.5, 2 Hz, C_{10}-βH), 1.91(1H, t/quintet, *J*=15.5, 3 Hz, C_5-H), 1.94-2.02(2H, m, C_6-H and C_7-H), 2.17(1H, d/m, *J*=14.5 Hz, C_2-αH), 2.23(1H, d/d/d, *J*=19, 11, 8.5 Hz, C_9-H), 2.26(1H, d/d, *J*=14.5, 8.5 Hz, C_2-βH), 2.28-2.38(2H, m, C_5-H and C_9-H), 5.66(1H, d/d/d/d, *J*=12, 8.5, 4, 3 Hz, C_3-H), 5.84(1H, d/d/d/d, *J*=12, 9, 4, 3 Hz, C_4-H); ^{13}C-NMR($CDCl_3$)δ: 18.5(q), 20.6, 27.9, 34.9, 35.7, 42.3(each t), 64.5, 128.5, 131.8(each d), 40.3, 217.9(each s).

15) Three deuterium atoms were incorporated in each isomer on treatment with deuterium oxide-potassium carbonate in refluxing tetrahydrofuran.

16) The stereochemistry of the ring juncture was tentatively assigned on the basis of the generalization that the *trans* isomer is more stable than the *cis* isomer in most bicyclo[5.3.0]decanes containing carbonyl function adjacent to the ring junction; see J.H. Rigby, Tetrahedron Lett., 1982, 1863, and references cited therein.

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