Communications to the Editor

[Chem. Pharm. Bull. 33(6)2594—2597(1985)]

AN EFFICIENT AND STEREOCONTROLLED SYNTHESIS OF A *CIS*- AND *TRANS*-FUSED BICYCLO[5.4.0]UNDECANE RING SYSTEM *VIA* INTRAMOLECULAR [2+2] PHOTOCYCLOADDITION

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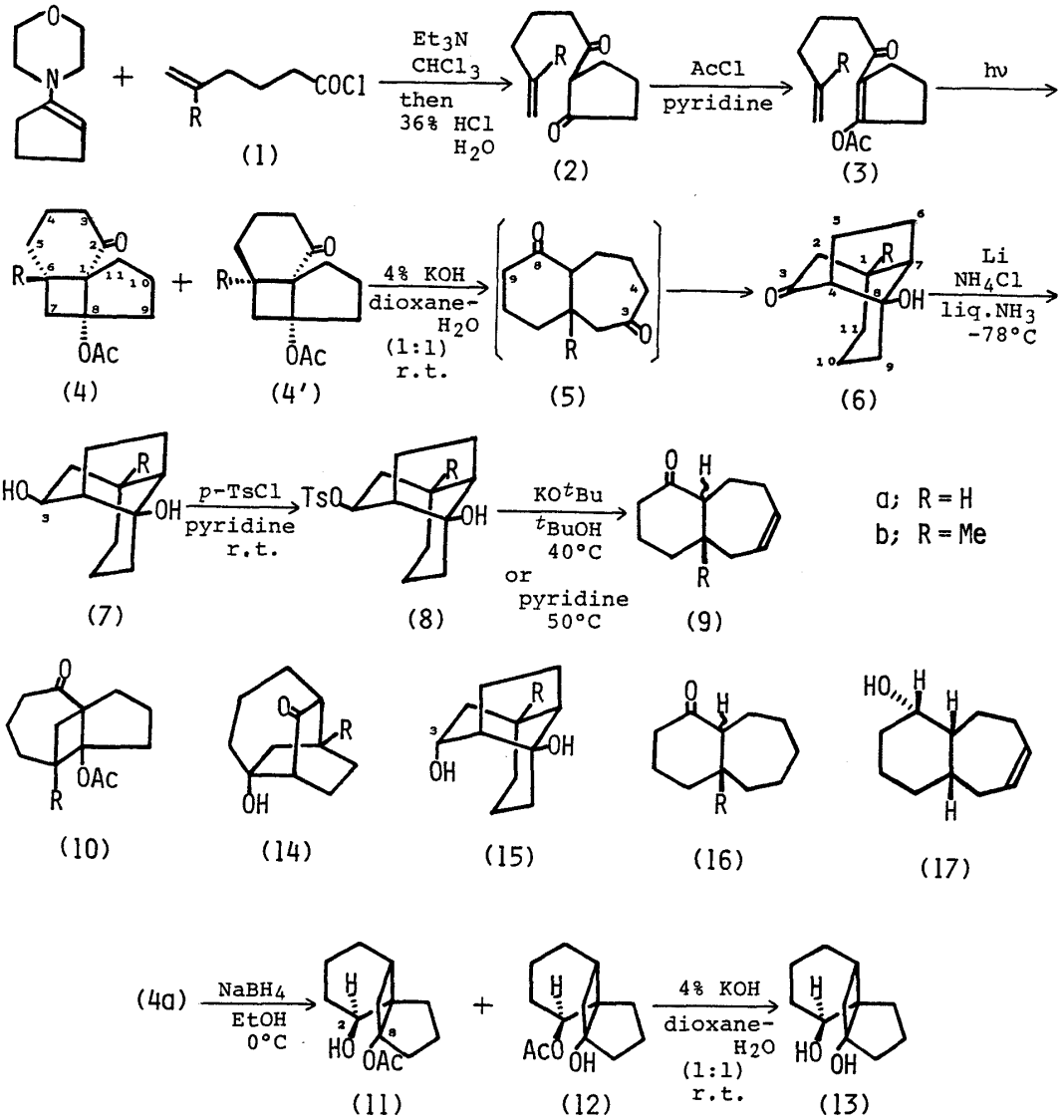
A five step synthesis including highly regioselective intramolecular [2+2] photocycloaddition of 1-acetoxy-2-(hex-5-enoyl)-cyclopentene species leads to *cis*- and *trans*-fused bicyclo[5.4.0]-undec-3-en-8-one species in excellent stereocontrolled manner.

KEYWORDS —— intramolecular [2+2] photocycloaddition; retro- and re-aldolization; Grob fragmentation; bicyclo[5.4.0]undec-3-en-8-one; 1-methylbicyclo[5.4.0]undec-3-en-8-one

Recently, many terpenes with a bicyclo[5.4.0]undecane moiety have been isolated from various natural sources, *e.g.*, classes of himachalane,[2a] dolastane,[2b] and cyathane[2c]. Some of them show interesting pharmacological properties including spasmolytic and antibiotic activities. However, in contrast to numerous works to date on the synthesis of fused carbobicycles such as hydroindane, hydroazulene, and decaline systems, there have been only a few reports on the synthesis of the bicyclo[5.4.0]undecane system,[3] and it remains a synthetic problem to control the stereochemistry of the ring fusion. We herein report a stereocontrolled synthesis of two new bicyclo[5.4.0]undec-3-en-8-ones, (9a) and (9b), that consists of intramolecular [2+2] photocycloaddition of 1-acetoxy-2-(hex-5-enoyl)cyclopentenes and subsequent skeletal transformation of photoproducts through retro- and re-aldolization followed by Grob fragmentation.[4] The synthetic potentiality of this method has been realized by the completely stereoselective construction of the thermodynamically disfavored *cis*-fused bicyclo[5.4.0]undecane system which is of critical importance in the synthesis of himachalane members.

Despite the well-documented synthetic utility of the intramolecular [2+2] photocycloaddition of cyclic α,β-enones to olefins, there are a limited number of the foregoing works[5] dealing with 1,7-diene variants, where they underwent photocycloaddition with competing reactions and poor regioselectivity resulting in low yield. The photolysis of our 1,7-diene variant, 1-acetoxy-2-(hex-5-enoyl)-cyclopentenes (3a,b), was conducted under high synthetic control to yield the parallel cycloaddition products. The materials, (3a) [bp 68-71 °C/0.001mmHg] and (3b) [bp 76-80 °C/0.002mmHg], were readily prepared from acid chlorides (1a,b) and

1-morpholinocyclopentene by standard procedures[4a] in 69 and 64% overall yields, respectively.[6] Irradiation of (3a) in ethyl acetate [*ca.* 2.0 x 10^{-2} M solution, 300 W medium-pressure Hg lamp, Pyrex filter, in Ar, 5-10°C, *ca.* 30 h] yielded photoadducts (4a) [87%, mp 32°C, IR(CCl_4) 1742, 1700 cm^{-1}, ^{1}H-NMR($CDCl_3$)δ: 1.99(3H, s)] and (4a') [0.7%, mp 99.5-100°C, IR(CCl_4) 1740, 1720 cm^{-1}, ^{1}H-NMR($CDCl_3$)δ: 2.10(3H, s)], after separation by silica gel column chromatography.



(1) (2) (3) (4) (4′) (5) (6) (7) (8) (9) (10) (14) (15) (16) (17) (11) (12) (13)

The structure of the minor adduct (4a') was determined by X-ray crystallographic analysis.[7] The structure of the major adduct (4a) was deduced from the following chemical transformations. (A) Alkaline hydrolysis of (4a) afforded a ketol (6a) (*vide infra*) that was identical with one from (4a'), thereby suggesting that both photoproducts have the same carbon framework. (B) Reduction [$NaBH_4$, EtOH, 0°C, 3.5 h] of (4a) gave the diol monoacetates (11) [12%, oil, ^{1}H-NMR($CDCl_3$)δ: 2.05(3H, s), 3.73(1H, m)] and (12) [80%, oil, ^{1}H-NMR($CDCl_3$)δ: 2.08(3H, s), 4.98(1H, t, *J*=7.8 Hz)], both of which afforded the same diol (13) [quant., oil, ^{1}H-NMR($CDCl_3$)δ: 3.87(1H, t, *J*=5.7 Hz)] on hydrolysis [4% KOH, dioxane/H_2O, 1:1, r.t.]. It is obvious that (12) resulted from acetyl migration from C_8-OH to C_2-OH in (11), which

indicates that the stereochemistry of the 5-4 ring juncture in the major epimer is *cis*. Thus, the major epimer was assigned to the formula (4a) as the C_6-epimer of (4a'). Similarly, irradiation of the 5'-methyl analogue (3b) afforded only the parallel adducts (4b) [84%, mp 81.5 °C, IR(CCl_4) 1742, 1697 cm^{-1}, ^{1}H-NMR($CDCl_3$)δ: 1.07(3H, s), 2.00(3H, s)] and (4b') [2.5%, mp 123.5 °C, IR(CCl_4) 1740, 1723 cm^{-1}, ^{1}H-NMR($CDCl_3$)δ: 1.23(3H, s), 2.03(3H, s)]. In both (3a) and (3b), the cross adducts (10a,b) could not be detected (HPLC).

Alkaline hydrolysis [4% KOH, dioxane/H_2O, 1:1, r.t.] of the mixture (4a+4a') gave the tricyclic ketol (6a)[8] [quant., mp 124 °C, IR($CHCl_3$) 3580, 3400, 1693 cm^{-1}]. The spectral data of this ketol suggested the two alternative structures (6a) and (14a) as a result of the C_4 to C_8 or the C_9 to C_3 re-aldolization of the transient retro-aldol intermediate, bicyclo[5.4.0]undecane-3,8-dione (5a), but the latter was ruled out in the next stage (*vide infra*). Similar treatment of the mixture (4b+4b') also afforded the ketol (6b) [99%, mp 168-169 °C].

The ketols (6a,b) were respectively converted to the bicyclo[5.4.0]undecanes (9a,b) through the C_4-C_8 bond cleavage by the following procedures. Reduction [Li, liq.NH_3-THF, NH_4Cl, -78 °C] of (6a) according to Rautenstrauch's modified procedure[9] afforded an equatorial alcohol (7a) [93%, mp 128-130 °C, ^{1}H-NMR($CDCl_3$)δ: 4.41(1H, ddd, *J*=10.3(ax-ax), 7.0, 3.8 Hz, C_3-H] together with a small amount of an axial alcohol (15a) [1.2%, mp 153.5 °C, ^{1}H-NMR($CDCl_3$)δ: 3.97(1H, dt, *J*=6.8, 2.5 Hz, C_3-H)]. The coupling patterns of the C_3-H nmr signals of these diols made their stereochemistry evident and ruled out the alternative structure (14a) for the starting ketol (6a) mentioned above. Basic treatment [KO^{t}Bu, ^{t}BuOH, 40 °C] of the diol monotosylate (8a) [88%, mp 72.5 °C] prepared by tosylation [1.3 equiv. of *p*-TsCl, pyridine, r.t., overnight] of (7a) readily caused Grob fragmentation[10] to give the target compound, bicyclo[5.4.0]undec-3-en-8-one (9a) in 84% yield as a C_7-epimeric mixture [*cis*:*trans*=15:85. *cis*-(9a): oil, IR(CCl_4) 1708 cm^{-1}, ^{1}H-NMR($CDCl_3$)δ: 1.36-2.83(14H), 5.50-5.94(2H). *trans*-(9a): oil, IR(CCl_4) 1711 cm^{-1}, ^{1}H-NMR($CDCl_3$)δ: 1.12-2.52(14H), 5.53-6.02(2H)] which was separated by HPLC (Nucleosil 50-5, hexane:EtOAc=30:1) into pure epimers. The stereochemistry of the ring fusion of each epimer was established by leading to the respective known saturated ketones, *cis*-(16a)[11] and *trans*-(16a)[11], by catalytic hydrogenation [1atm H_2, PtO_2, Et_2O, r.t,]. On the other hand, this fragmentation was also accomplished with hot pyridine [50 °C, 35 h, 96%], where the thermodynamically disfavored *cis* epimer became dominant (*cis*:*trans*=90:10). This is attributed to decreased epimerization of initially formed *cis*-(9a) under the milder basic condition. Furthermore, the completely stereocontrolled construction of *cis*-(9a) was performed as follows. Treatment of (8a) with lithium aluminum hydride [THF, 0 °C] caused the fragmentation and subsequent reduction of the carbonyl function of *cis*-(9a) without epimerization to give an alcohol (17) [mp 87-88.5 °C, ^{1}H-NMR($CDCl_3$) δ: 3.70(1H, dt, *J*=10.3, 4.6 Hz), 5.43(2H, m)] exclusively, oxidation of which by molecular sieve-pyridinium chlorochromate[12] [PCC, 3-Å molecular sieve, CH_2Cl_2, 0 °C, 0.5 h] furnished *cis*-(9a) in 88% overall yield. Similarly, the ketol (6b) was successively treated under the same procedures as (6a) to yield (7b) [quant., mp 115-120 °C], (8b) [92%, mp 88-88.5 °C], and the final product 1-methylbicyclo-[5.4.0]undec-3-en-8-one (9b) [KO^{t}Bu, ^{t}BuOH; 88%, *cis*:*trans*=22:78. pyridine; 98%, exclusively *cis*.[13] *cis*-(9b): oil, IR(CCl_4) 1707 cm^{-1}, ^{1}H-NMR($CDCl_3$)δ: 1.00(3H,

s), 1.32-2.59(13H), 5.59(1H, dt, J=11, 6.5 Hz), 5.84(1H, dt, J=11, 5.5 Hz). *trans*-(9b): oil, IR(CCl_4) 1712 cm^{-1}, ^{1}H-NMR($CDCl_3$)δ: 0.75(3H, s), 1.07-2.51(13H), 5.46-6.11(2H)].

Thus, the new bicyclo[5.4.0]undecanes (9a,b) were synthesized from easily accessible enol esters (3a,b) in excellent overall yield and in highly stereocontrolled manner. The present method provides a useful tool for synthesis of himachalane type sesquiterpenes, and tricyclic diterpenes possessing a bicyclo[5.4.0]undecane skeleton as well, since the C_8 carbonyl and C_3-C_4 double bond functions serve as important access for further constructions. The application of this method to the syntheses of natural products is now in progress.

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4) For our earlier studies on the photochemistry of the lower homologues, 1-acetoxy-2-(pent-4-enoyl)cyclopentenes, and skeletal transformation of the photoproducts, see a) H. Seto, Y. Fujimoto, H. Yoshioka, and T. Tatsuno, Chem. Pharm. Bull., 32, 3751 (1984); b) H. Seto, S. Hirokawa, Y. Fujimoto, and T. Tatsuno, Chem. Lett., 1983, 989; c) H. Seto, M. Sakaguchi, Y. Fujimoto, T. Tatsuno, and H. Yoshioka, Chem. Pharm. Bull., 33, 412 (1985).
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6) The compounds (3a,b) contained a large amount of the corresponding *exo*-cyclic enol esters (*Z*- and *E*-forms), respectively. However, this did not affect the subsequent photoaddition because of concurrent equilibration among these isomers under irradiation and the substrate-specificity of the cycloaddition to *endo*-isomers (3a,b); for a close analogy, see ref. 4a.
7) We thank Miss. K. Kobayashi (this institute) for her help with the X-ray analysis. The details will be reported in a full paper.
8) The positional numbers in this tricycloundecane system are employed as a matter of convenience.
9) Reduction was carried out in the presence of NH_4Cl, and three batches of NH_4Cl and Li were added alternately; see V. Rautenstrauch, B. Willhalm, and W. Thommen, Helv. Chim. Acta, 46, 2109 (1981). By a normal procedure the equatorial alcohol (7a) was obtained predominantly but in low stereoselectivity and in incomplete conversion. On the other hand, $NaBH_4$, $LiAlH_4$, Raney-Ni, and MPV reductions of (6a) mainly afforded the axial alcohol (15a).
10) For the mechanism and stereochemistry on this one-step synchronous fragmentation, see P. Deslongchamps, "Stereoelectronic Effects in Organic Chemistry," Pergamon Press, Inc., New York, 1983, pp. 257-266.
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13) The fragmentation was caused more easily than the case of (8a) [40°C, 25 h], and the stereoselectivity was little affected by elongation of the reaction time [*ca.* 35 h].

(Received April 2, 1985)