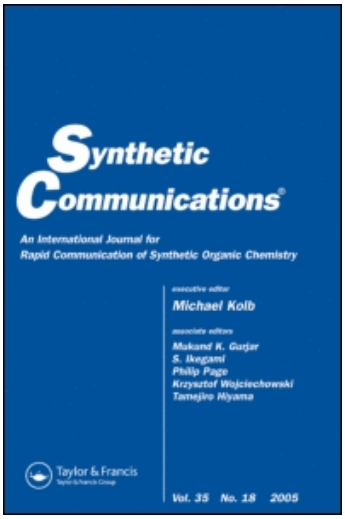

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Stereoselective Synthesis of *cis*- and *trans*-Bicyclo [6.3.0] undec-4-en-10-ones. Efficient Precursors of 4-Oxo-1,2-Cyclopentane Dipropanoic Acids

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STEREOSELECTIVE SYNTHESIS OF cis- AND trans-BICYCLO [6.3.0] UNDEC-4-EN-10-ONES. EFFICIENT PRECURSORS OF 4-OXO-1,2-CYCLOPENTANE DIPROPANOIC ACIDS

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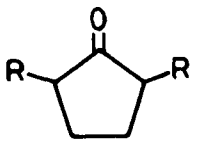
ABSTRACT: Short syntheses of title compounds from cheap, readily available cis, cis-1,5-cyclooctadiene are described.

Substituted cyclopentanones of well defined stereochemistry are very useful synthons in a wide variety of natural product synthesis. While α,α'- and α,β -disubstituted cyclopentanones 1 and 2, respectively, are quite readily accessible through the expedient of alkylations and conjugate additions, among other methods, entry into the β,β'-disubstituted derivatives 3 requires more involved methodology.[1]



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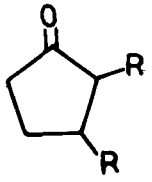

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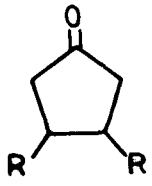

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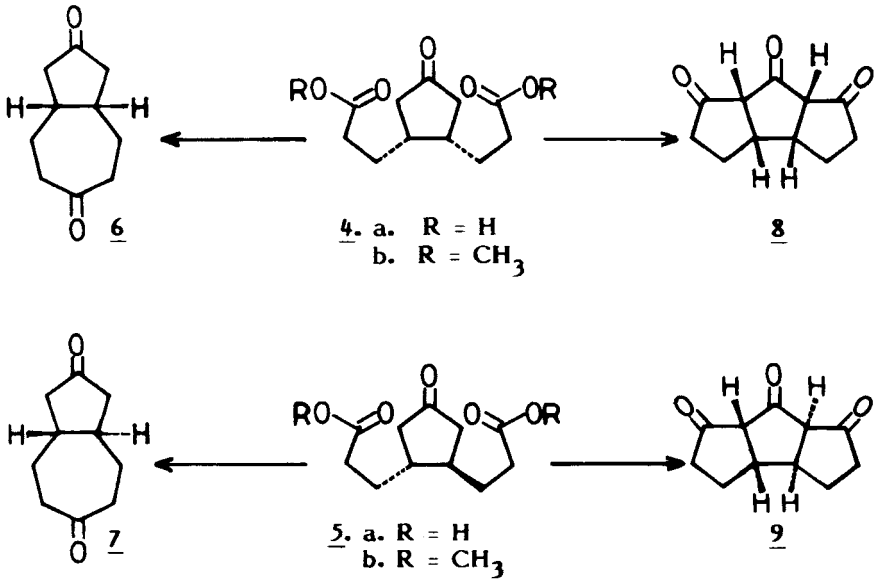
In connection with some ongoing projects in our laboratory, we required cis-4a- and trans-4-oxo-1,2-cyclopentanedipropanoic acids 5a as precursors for perhydroazulenes 6 and 7 as well as triquinanes 8 and 9, respectively, Scheme 1.[2,3]

We describe here a simple and convenient route to 4a,b and 5a,b from cheap, abundantly available cis, cis-1,5-cyclooctadiene 10. Our synthesis proceeds via the intermediacy of cis-11 and trans-bicyclo[6.3.0]undec-4-en-10-ones 12, compounds of considerable interest in their own right.[4]

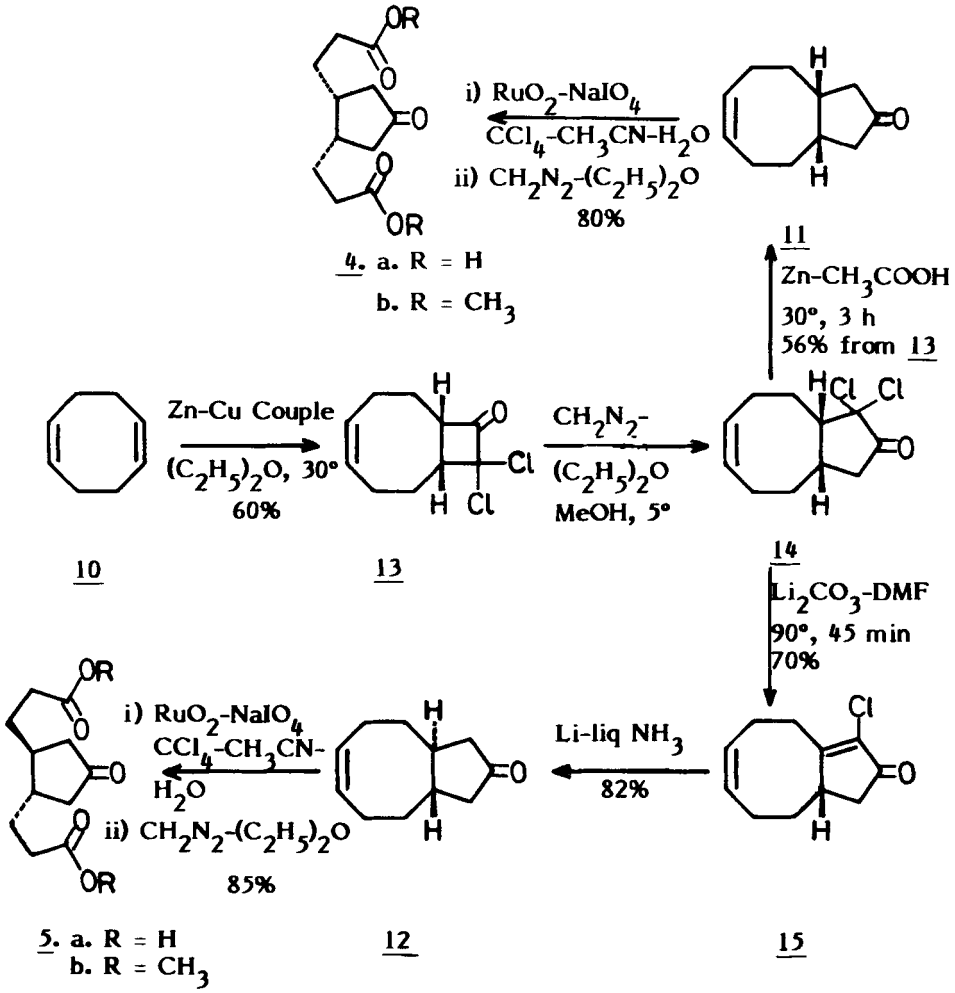
Scheme 1



Our synthetic route to 4a,b from 10 is depicted in Scheme 2 and involves the Greene cyclopentanone annulation methodology[6]

as the key step. The cis-bicyclo[6.3.0] undec-4-en-10-one 11 obtained in three steps from 10, undergoes smooth oxidative cleavage of the double bond with ruthenium dioxide according to the procedure of Sharpless[7] to furnish the desired cis-diacid 4a. The diacid 4a with

Scheme 2



diazomethane is converted to dimethyl ester 4b which is more conveniently characterised. The preparation of the trans- series required the generation of the ring junction stereochemistry under thermodynamic control[8]. In this context, the α,α-dichloro-cyclopentanone 14 was first dehydrohalogenated to the α-chloroenone 15. Reduction of 15 with Li-liq NH_3 furnished the desired trans- bicyclic enone 12 in good yield. Once again ruthenium dioxide oxidation led to the trans-diacid 5a and was esterified to the methyl ester 5b for full characterisation, scheme 2.

Experimental Section

^1H NMR and ^{13}C NMR spectra were obtained on a JEOL FX-100 spectrometer. All chemical shifts are reported in units relative to Me_4Si in $CDCl_3$ solution. In the ^{13}C NMR spectral data off resonance multiplicities are given in parentheses. Infrared spectra were recorded on Perkin-Elmer 293 spectrophotometer. All solvent extracts were washed with brine and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure on Buchi-EL rotavapor.

10,10-Dichlorobicyclo[6.2.0]dec-4-en-9-one(13):[9,10] A solution of freshly distilled trichloroacetylchloride (18 g, 0.1 mol) in 400 ml of dry ether was added over a period of 3 h to a vigorously stirred mixture of 1,5-cyclooctadiene (50 g, 0.46 mol) and activated Zn-Cu couple (19 g) in 400 ml of dry ether under a nitrogen atmosphere. The reaction mixture was further stirred for 6 h. The Zn-Cu couple

was filtered off and ether layer was washed successively with water, sodiumbicarbonate and dried. The solvent was removed and excess 1,5-cyclooctadiene distilled off under reduced pressure. Purification on silica gel column furnished the ketene adduct 13 (13 g, 60%) b.p. 120°C/0.5 torr, IR (neat) 1800, 1650 cm^{-1}; ^{1}H NMR:δ 5.64(br,S,1H), 3.88-3.52(m,1H), 3.2-2.8(m,1H), 2.6-1.8(m, 8H); ^{13}C NMR:δ 196.73(s), 130.33(d), 129.92(d), 88.0(s), 58.58(d), 49.66(d), 24.17(t),25.36(t), 25.06(t), 24.12(t).

11,11-Dichlorobicyclo[6.3.0]undec-4-en-10-one(14): To a solution of 13 (3 g, 0.0137 mol) in 30ml of ether and a catalytic amount of methanol, was added an ethereal solution of diazomethane. The reaction mixture was kept at ~ 5°C for 1h and excess diazomethane destroyed with a few drops of acetic acid. Removal of solvent furnished the crude compound 14 (3.3 g) which was used as such for the next reaction.

cis-Bicyclo[6.3.0]undec-4-en-10-one (11): To a vigorously stirred mixture of 14 (3.3 g) in 20 ml of acetic acid was slowly added 4 g of Zn powder. The reaction mixture was stirred at r.t. for further 3h. The solid residue was filtered off and excess acetic acid removed under reduced pressure. The residue was taken in ether and ethereal layer washed with water, sodiumbicarbonate and dried. Removal of solvent and purification on silica gel column furnished 11 (1.26 g, 56% from 13), b.p. 100°C/1 torr. IR (neat), 1740, 1660, 690 cm^{-1}; ^{1}H NMR, δ 5.8-5.4 (m, 2H), 2.9-1.4 (m, 14H); ^{13}C δ 218.40(s), 128.16(d),

45.08(t), 38.98(d), 28.94(t), 27.59(t); Anal. Calcd for $C_{11}H_{16}O$: C, 80.44, H, 9.83; Found: C, 79.21, H,9.74%.

cis-4-Oxo-1,2-cyclopentane dipropanoic acid (4a) and cis-4-oxo-1,2-cyclopentane dipropanoic dimethyl ester (4b).[3] To a mixture of compound 11 (0.159 g, 0.97 mmol) in 2 ml of carbon tetrachloride, 2 ml of acetonitrile, 3ml of water and sodium periodate (900 mg, 4.2 mmol) was added rutheniumdioxide (6 mg, 0.045 mmol). The reaction mixture was vigorously stirred for 7h at r.t. and diluted with 50 ml of ethyl acetate and stirred for 45 min. The reaction mixture was filtered through a celite pad, and the aqueous phase saturated with brine and extracted thoroughly (20 ml x 3) with ethyl acetate. The combined organic extract was dried and removal of solvent furnished the crude diacid 4a (0.215 g).[3]

The total diacid 4a was dissolved in 10 ml of methanol and an ethereal solution of diazomethane was added to it at 0°C until a pale yellow colour persisted. The reaction mixture was kept at 0°C for 15 min and excess diazomethane destroyed with a few drops of acetic acid. Removal of solvent and purification on silica gel column furnished the diester 4b (0.20 g, 80%),[3] b.p. 150°C/0.3 torr. IR (neat) 1740, 720 cm^{-1}; ^1H NMR: δ 3.66(s, 6H), 2.5 - 1.3(m, 14H); ^{13}C NMR: δ 216.62(s) 172.84(s), 51.01(q), 42.38, 38.04, 31.64, 23.89.

11-Chlorobicyclo[6.3.0]undec-1,4-en-10-one (15): A solution of the dichloroketone 14 (6.7 g, 0.028 mol) and Li_2CO_3 (9.6 g, 0.129 mol)

in 180 ml of dry DMF was vigorously stirred at 90°C under a nitrogen atmosphere for 45 min. The reaction mixture was diluted with 250 ml water and extracted with ether (50 ml x 5). The ether extract was washed, dried and concentrated to give an oil (5.4 g) which was chromatographed on silica gel column to furnish 15 (3.7 g, 70% from (13), b.p. 140°C/0.5 torr, IR (neat): 1720, 1610 cm^{-1}; ^1H NMR: δ 5.9-5.4 (m, 2H), 3.5-1.2(m,11 H); ^{13}C NMR: δ 199.49(s), 176.42(s), 132.92(s), 128.86(d), 128.75(d), 41.97(t), 40.33(d), 35.28(t), 30.82(t), 25.42(t), 24.95(t). Anal. Calcd for $C_{11}H_{13}ClO$: C, 67.18, H, 6.66; Found: C, 67.20, H, 6.78%.

trans-Bicyclo[6.3.0]undec-4-en-10-one (12): A solution of the monochloroenone 15 (1 g, 5.2 mmol) in 10 ml of dioxane and 10 ml of ether was added over a period of 7 min to a solution of ~ 100 ml of ammonia containing lithium (0.65 g, 92.9 mmol). The solution was stirred for an additional 10 min and then quenched with ammonium chloride. The ammonia was evaporated off and the remaining mixture diluted with water and extracted with ether (50 ml x 3). The organic layer was washed, dried, and concentrated to yield a mixture of 12 and some corresponding alcohol formed during the reaction (0.885 g). The total mixture obtained from the above reaction in 7 ml of CH_2Cl_2 was added dropwise to a suspension of PCC (1.25 g, 5.8 mmol) and molecular sieves (3 g) in 5 ml of CH_2Cl_2 and vigorously stirred for 45 min at r.t. It was diluted with 30 ml of ether, filtered through fluorosil and the black residue washed with ether. The combined filtrate was concentrated and distilled (~ 100°C/0.5 torr) to furnish

the pure compound 12 (0.705 g, 82%), IR (neat) 1750, 1650, 720 cm^{-1}, ^1H NMR: δ 5.8-5.4(m,2H), 2.7-1.0(m,14H); ^{13}C NMR: δ 218.04(s), 129.63(d), 47.14(t), 39.57(d), 35.87(t), 24.59(t); Anal. Calcd for $C_{11}H_{16}O$), C, 80.44, H, 9.83; Found: C, 80.76; H, 10.33.

trans-4-Oxo-1,2-cyclopentane dipropanoic acid (5a) and trans-4-oxo-1,2-cyclopentane dipropanoic dimethyl ester (5b): To a mixture of compound 12 (0.620 g, 3.75 mmol) in 7.5 ml of carbon tetrachloride, 7.5 ml of acetonitrile, 11.3 ml of water and sodium periodate (3.5 g, 16.3 mmol) was added ruthenium dioxide (23 mg, 0.17 mmol). The reaction mixture was vigorously stirred for 9 h at r.t. and diluted with 100 ml of ethyl acetate and stirred for 45 min. It was filtered through a celite pad and the aqueous phase saturated with brine and extracted thoroughly (25 ml x 5) with ethyl acetate. The combined organic extract was dried and concentrated to furnish the crude diacid 5a (0.817 g).

The total diacid 5a (0.815 g) was dissolved in 20 ml of methanol and an ethereal solution of diazomethane was added to it at 0°C until a pale yellow colour persisted. The reaction mixture was kept at 0°C for 15 min and excess diazomethane destroyed with a few drops of acetic acid. Removal of solvent and filtration on silica gel column furnished the trans diester 5b (0.83 g, 85%), b.p. 150°C/0.3 torr, IR (neat) 1740 cm^{-1}; ^1H NMR: δ 3.56(s,6H), 2.6-1.4(m,14 H); ^{13}C NMR: δ 216.40(s), 173.37(s), 51.60(q), 44.50, 41.97, 32.46, 28.88; Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92, H, 7.87; Found: C, 60.5, H, 7.98%.

Acknowledgement: We thank CSIR and UGC for support under the Special Assistance Programme in Organic Chemistry.

References and Notes:

1. Most of the methodologies to substituted cyclopentanones have been developed in the context of cis-jasmone, methyl cis-jasmonate, prostanoids, methylenomycin type of cyclopentanoid natural products. For some of the leading references, see, R.A. Ellison, Synthesis, 1973, 397; T.L. Ho, Synth. Commun., 1974, 4, 265; A. Mitra, The Synthesis of Prostaglandin Derivatives, John Wiley and Sons, N.Y., 1978; S.M. Roberts and R.F. Newton, Prostaglandins and Thromboxanes, Butterworths Scientific, London, 1982; A. Terahara, T. Haneishi and M. Arai, Heterocycles, 1979, 13, 353.

2. This compound has been previously reported[3] by a different, longer route and applied to the synthesis of all cis-triquinane trione 8.

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