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A FACILE RING-OPENING REACTION OF CYCLOBUTENES: APPLICATION TO A SYNTHESIS OF VITAMIN D_3

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Abstract—The extraordinary accelerating effects of arylsulfinyl, arylsulfonyl, and diphenylphosphinoyl carbanion substituents for cyclobutene ring-opening reaction of bicyclo[4.2.0]-oct-1(6)-ene derivatives are described. The scope and limitation of this new type of reaction, and the application of the dienes so generated by this method for the synthesis of vitamin D_3, are also discussed.

Because of the important therapeutic value of vitamin D in treating disorders of calcium and phosphorus metabolism, considerable attention has been directed toward the chemistry of vitamin D causing the discover of high biologically active vitamin D derivatives[1] and increased activity in its synthetic chemistry.[2] Recently it has become clear that the primary requirement for activity in vitamin D analogues is the presence of a 1α-hydroxyl group[3] and synthetic 1α-hydroxycholecalciferol (1) is now being used in the clinical treatment of nephritic bone disease in humans.[4] Because of these facts, much attention has been focussed on the synthesis and reactivity of A-ring having diene system of vitamin D.

The thermal ring opening reaction of cyclobutenes (eqn 1) has been proven to be one of the most useful reactions for generating such diene systems and widely used in the synthesis of natural products.[5] Our entry to such systems is based on the observations on the exceptionally facile ring-opening reaction of cyclobutenes, facilitated by arylsulfinyl, arylsulfonyl, and diphenylphosphinoyl carbanions (eqn 2). Especially, the finding of the last case (eqn 2) enabled us to apply this reaction to the synthesis of vitamin D series.

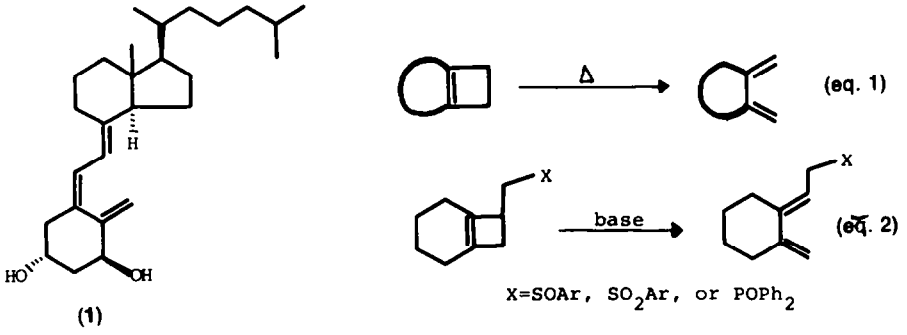
Here, we wise to report the anion facilitated ring opening reactions of cyclobutenes and its application to a synthesis of vitamin D_3 with full experimental details.[6]

RESULTS AND DISCUSSION

Ring-opening reactions of cyclobutenes facilitated by arylsulfinyl and arylsulfonyl carbanions.

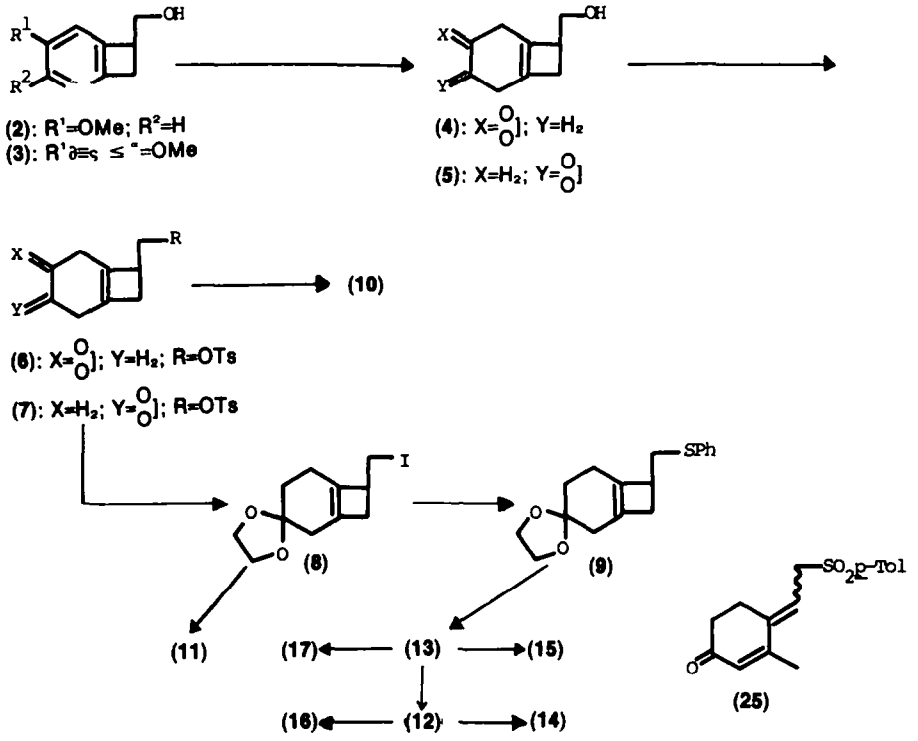
The synthesis of compounds (10)–(17), was straightforward (Scheme 2). Birch reduction of benzocyclobutenylmethyl alcohols (2)[7] and (3),[8] followed by ketalization, afforded (4) and (5) respectively which were subsequently treated with tosyl chloride in pyridine to give tosylates (6) and (7). Each compound (10 and 11) was prepared by a reaction of (6) with sodium toluene-p-sulfinate in the presence of sodium iodide and by treating (8), which was derived from (7), with sodium toluene-p-sulfinate. The compounds (13) and (12) were obtained from (8) through (9) by successive treatment with sodium thiophenolate and 1 and 2 equiv of m-chloroperbenzoic acid, respectively. The cyclobutenes thus obtained were subjected to the ring-opening reaction and the results are shown in Table 1.

A very attractive feature of this method of diene generation is that alkylation of (13) and (12), involving essentially the same conditions as for ring-opening reac-



(1)

Scheme 1.



Scheme 2.

Table 1.

Entry	Cyclobutenes				Products						
	No.	X	Y	Z	No.	X	Y	Z	Yield %	No.	R / Yield %
1	10	O	H₂	CH_2SO_2-*p*-Tol	18	O	H₂	CH_2SO_2-*p*-Tol	58		—
2	11	H₂	O	CH_2SO_2-*p*-Tol	19	H₂	O	CH_2SO_2-*p*-Tol	90		—
3	12	H₂	O	CH_2SO_2Ph	20	H₂	O	CH_2SO_2Ph	92		—
4	13	H₂	O	CH_2SOPh	21	H₂	O	CH_2SOPh	46.5	22	H / 50
5	14	H₂	O	$CH(Me)SO_2Ph$	23	H₂	O	$CH(Me)SO_2Ph$	31		—
6	15	H₂	O	$CH(Me)SOPh$						24	Me / 70
7	16	H₂	O	$C(Me)_2SO_2Ph$							
8	17	H₂	O	$C(Me)_2SOPh$							

tions of cyclobutenes, n-BuLi/THF, can be carried out at −78°, at which temperature the cyclobutene ring remains intact. Thus, compounds (15) and (14) were obtained from (13) and (12), respectively, in almost quantitative yield by using 1.2 equiv of n-BuLi and 1.2 equiv of methyl iodide, and 2.2 equiv of base and electrophile were used for (17) and (16). The cyclobutene ring-opening was usually carried out at −30° by using n-BuLi as a base (Table 1) and the products obtained, for example, compound (19) showed typical exomethylene protons as a distorted triplet at δ5.4 in its NMR and was also converted into dienone (25) by treatment with acid for confirming the structure of (19). In case of sulfoxy compounds (13) and (15), the products which were formed by treating them under the same reaction conditions as for the sulfonyl compounds were (21), (22) and (24), respectively. The formation of (21) and (24) could be explained by the intervention of double [2,3] sigmatropic rearrangement of the initial products (26) and (27) via (28) and (29). Actually, the compound (22), which resulted from nucleophilic substitution of the phenyl group of compound (13) by n-butyl carbanion on treatment with n-BuLi followed by ring-opening, was transformed quantitatively into compound (31) on standing at room temperature via (30). In case of the compound (13), lithium diisopropylamide was also used as a base in place of n-BuLi under the same conditions to give compound (21) as sole product.

It is clear that the presence of an active hydrogen adjacent to the arylsulfinyl or arylsulfonyl group is critical for this new ring-opening reaction of cyclobutenes, since compounds (16) and (17), which have no active hydrogen, were recovered unchanged when subjected to the above treatment. Thus, we could establish the generality and limitation of a new method for generating the A-ring having labile diene system of vitamin D from rather stable cyclobutenes under extremely mild conditions. Our next task is the application of this new method for the synthesis of biologically important vitamin D_3 and will be discussed in the next section.

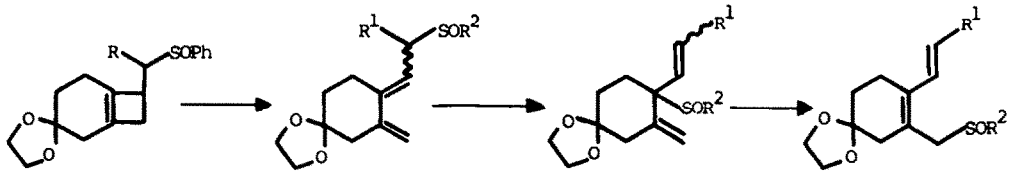
Ring-opening reactions of cyclobutenes facilitated by diphenylphosphinoyl carbanion. Total synthesis of vitamin D_3

From the outset of our work in the synthesis of vitamin D_3, we envisioned a direct application of cyclobutene ring-opening reaction facilitated by sulfonyl carbanion discussed in the preceeding section via Julia alkene synthesis[9] through compounds (35) (R = Ac, $MeSO_2$, p-Tos, etc.) leading to compound (36) as a model compound of vitamin D_3. Compound (32), which was prepared by the treatment of (10) with cyclohexanone under basic conditions, was subjected to the cyclobutene ring-opening reaction under the same reaction conditions as described in the preceeding section but failed to give compound (34). Then, the conversion of compound (34), which was obtained by the condensation of (18) and cyclohexanone under the same reaction conditions as for (32), into compounds (35) (R = Ac, $MeSO_2$, p-Tos) was tried but could not be achieved. This was also the case for the conversion of (32) into (33).[10]

Next, our attention turned to investigation of developing another type of activating group which is suitable for cyclobutene ring-opening reaction and also alkene synthesis. Several compounds were envisioned as potentially useful for this purpose and we chose diphenylphosphinoyl group as a promising activating group.[11] Before beginning the work on vitamin D_3, we first investigated the preparation of diphenylphosphinoylcyclobutenes and their ring-opening reactions. Thus compound (38) was prepared by treating (6) with NaBr in DMF, followed by successive treatment of the resulting bromide (37) with lithium diphenylphosphide and 5% H_2O_2. Compound (39) which was obtained by successive treatment of 2 with Na in liq. NH_3, tosyl chloride in pyridine, 10% HCl in acetone, and $NaBH_4$ in MeOH, reacted with benzoyl chloride in pyridine and then NaBr in DMF to give compound (40) which was converted into (41) by following the same procedure as for (37) to (38). Hydrolysis (NaOH, MeOH) of (41) afforded (42) which on reaction with ethyl vinyl ether gave compound (43).

Diphenylphosphinoylcyclobutenes (38), (41), (42) and (43) were subjected to the ring-opening reaction under the reaction conditions described in Table 2 and we learned that reaction proceeded smoothly in the same manner as arylsulfinyl and arylsulfonyl cases mentioned in the preceding section but prolonged reaction time was required.

Having a solution the first question if diphenylphosphinoyl carbanion facilitates the cyclobutene ring-opening reaction, we have carried out Horner reaction of phosphine oxide (44) with cyclohexanone, 2-methylcyclohexanone, and Grundmann's ketone[12] (49), and the triene (47),[13] (48)[13] and (50) were obtained. The geometry of triene systems of these compounds was assigned tentatively based on the NMR spectra (see Experimental) which are typical of triene system of *trans*-cholecalciferol.[2b] Since the direct conversion of compound (50) into *trans*-vitamin D_3 (55) via (51) was not achieved because of the instability of (50) on acid treatment, we made a detour to reach compound (55). Of the reported



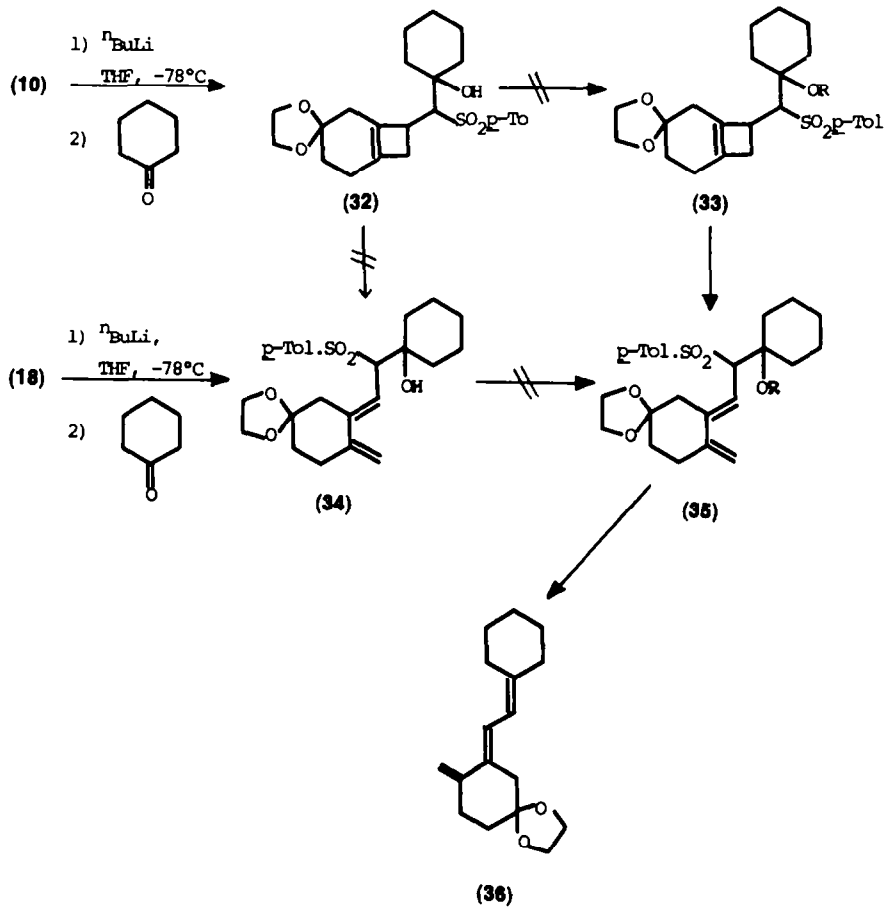
(13): R=H
(15): R=Me

(22): R¹=H, R²=ᵗBu
(26): R¹=H, R²=Ph
(27): R¹=Me, R²=Ph

(28): R¹=H, R²=Ph
(29): R¹=Me, R²=Ph
(30): R¹=H, R²=

(21): R¹=H, R²=Ph
(24): R¹=Me, R²=Ph
(31): R¹=H, R²=ᵗBu

Scheme 3.

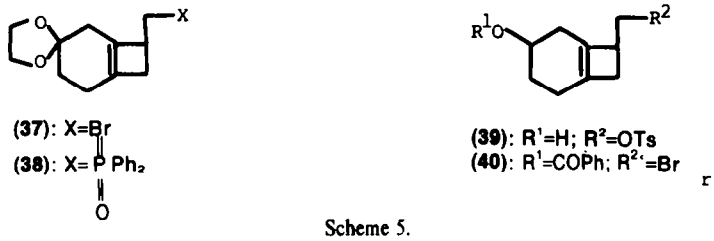


Scheme 4.

method[14] for protection of the labile triene part of vitamin D, cheletropic reaction of sulfur dioxide was envisioned as one of the useful methods because of easy manipulation and mild reaction conditions.[15] Sulfur dioxide adduct (52), prepared by treating (50) with sulfurous acid was hydrolyzed to give ketone (53) which on reduction with $NaBH_4$ afforded alcohol (54) as a diastereoisomeric mixture. The extrusion of sulfur dioxide of (54) effected by heating (54) in EtOH in the presence of $NaHCO_3$, gave *trans*-vitamin D_3 (55) after careful purification of the crude product. The product thus obtained was identical with the authentic sample pre-

Table 2.

Entry	Cyclobutenes			Products			
	No.	X	Y	No.	X	Y	Yield %
1	38	$-OCH_2CH_2O-$		44	$-OCH_2CH_2O-$		76
2	41	H	$-O_2CPh$	45	H	-OH	27
3	42	H	-OH	45	H	-OH	43
4	44	H	$-OCH(Me)OEt$	46	H	$-OCH(Me)OEt$	13



Scheme 5.

pared from vitamin D_3 (57) via sulfur dioxide adduct (56)[15a] followed by extrusion of sulfur dioxide.[16] Since the selective one-way isomerization of *trans*-vitamin D_3 (55) to vitamin D_3 (57) has been known,[17] this work constitutes also the total synthesis of vitamin D_3 (57).

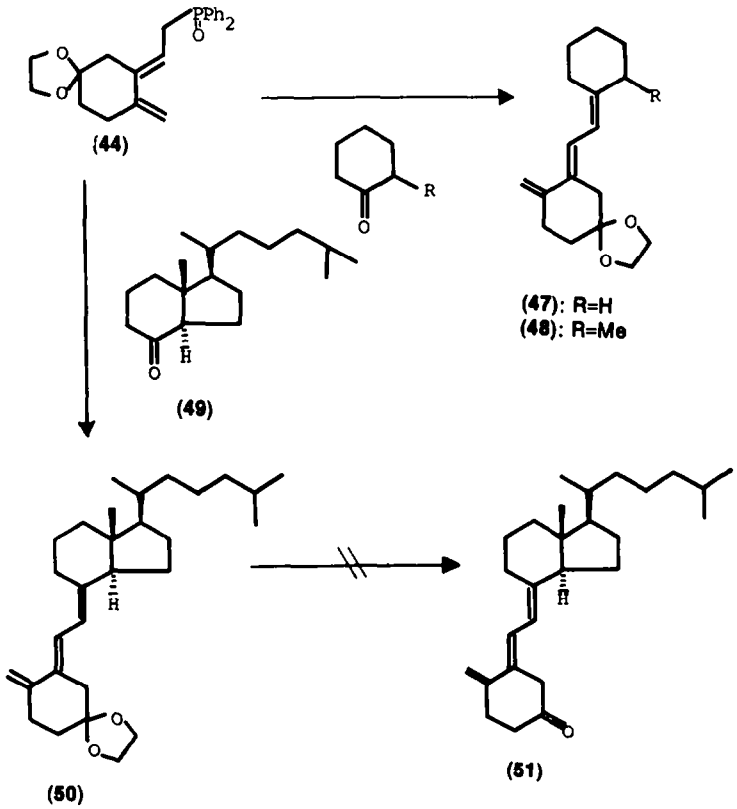
CONCLUSION

We disclose a new method for the generation of rather labile and reactive diene systems from chemically more stable cyclobutene derivatives, which have suitable functional groups (sulfinyl, sulfonyl, and diphenylphosphinoyl) for further manipulations, under extremely mild conditions. Electrophilic reaction at adjacent position to functional groups could be carried out under the same reaction conditions as for ring-opening reaction by simply controlling the reaction temperature. The diene system thus generated could be used efficiently for the synthesis of vitamin D_3.

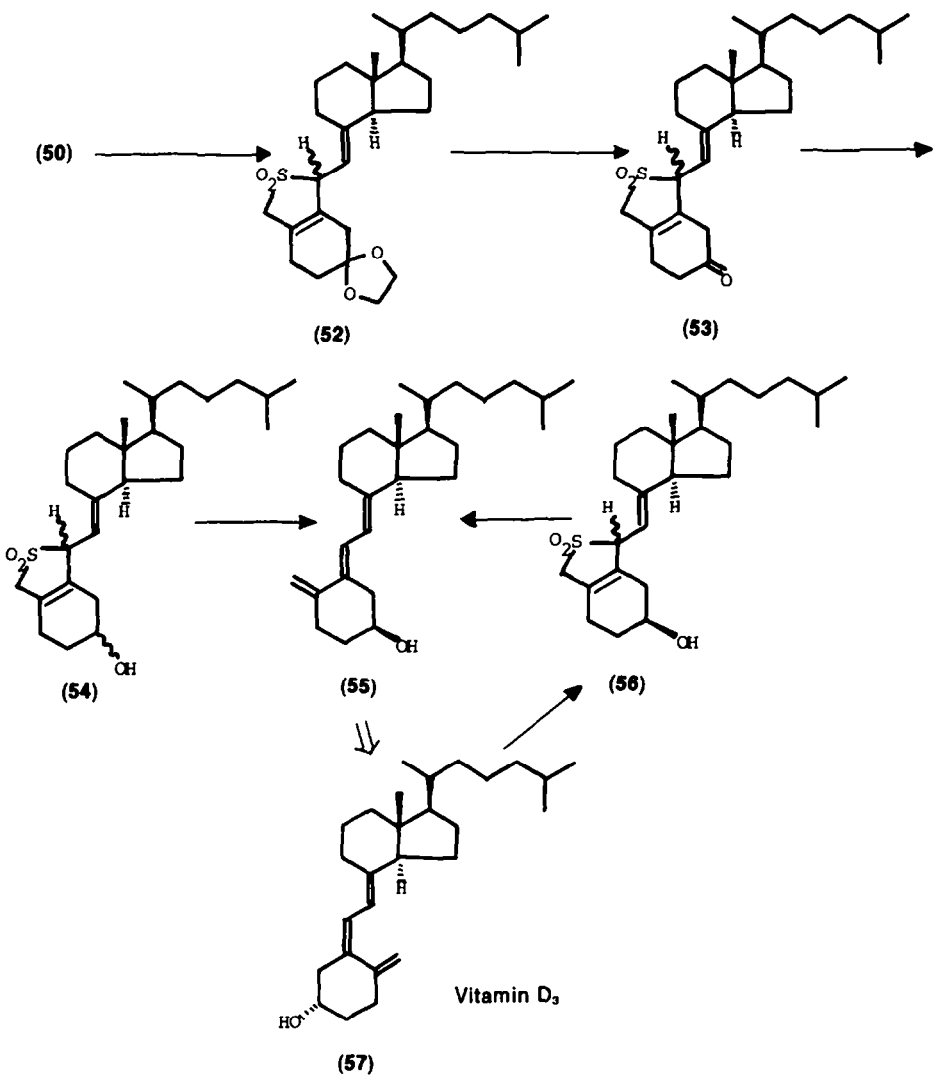
EXPERIMENTAL

General methods. All melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi EPI-3 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured on a JEOL JNM-PMX-60 spectrometer. Chemical shifts are reported as δ values relative to internal tetramethylsilane (Me_4Si). Mass spectra were taken on a Hitachi M-52G spectrometer. All optical rotations were measured in chloroform solution on a JASCO PIP-SL polarimeter using a 1-dm cell. Column chromatography was performed on silica gel. Anhydrous sodium sulphate was used for drying solutions.

4,4 - (*Ethylenedioxy*) - 7 - *hydroxymethylbicyclo*[4.2.0]*octa* - 1(6) - *ene* (4). To a stirred solution of 44 g (0.268 mol) of 5-methoxybenzocyclobutenylmethanol (2) in 1.5 L of liquid ammonia, 400 mL of anhydrous tetrehydrofuran, and 100 mL of anhydrous ethanol was added 14.0 g (0.609 mol) of sodium at −78°. Stirring was continued for 15 min at −78° and ethanol was then added to the reaction mixture. After evaporation of the solvent, water was added and the resulting mixture was extracted with benzene. The extract was evaporated to give the residue which was dissolved in 500 mL of dichloromethane. This solution was treated with 30 g (0.484 mol) of ethylene glycol and a catalytic amount of toluene-p-sulfonic acid for 1 h at room temperature under nitrogen. Usual work-up afforded a crude product which was chromatographed using chloroform as eluent to give 52 g (99%) of (4) as a colorless oil: IR ($CHCl_3$) 3600 cm^{-1}; NMR (CCl_4) δ3.55 (2H, dJ = 6 Hz, CH_2OH), 3.83 (4H, s, $-OCH_2$



Scheme 6.



Scheme 7.

CH_2O); MS *m/e*: 196 (M^+). (Found: C, 64.20; H, 7.80. Calc. for $C_{11}H_{16}O_3 \cdot 0.1CHCl_3$: C, 64.04; H, 7.80%).

3,3 - (*Ethylenedioxy*) - 7 - *hydroxymethylbicyclo*[4.2.0]*octa* - 1(6) - *ene* (**5**). 4-Methoxybenzocyclobutenylmethanol (**3**) (44 g) (0.268 mol) was converted into (**5**) by following the same method described above to give 52 g (99%) of (**5**) as a colorless oil: IR ($CHCl_3$) 3600 cm^{-1}; NMR (CCl_4) δ3.55 (2H, d, J = 6 Hz, CH_2OH), 3.86 (4H, s, $-OCH_2CH_2O-$); MS *m/e* 196 (M^+).

4,4 - (*Ethylenedioxy*) - 7 - *bromomethylbicyclo*[4.2.0]*octa* - 1(6)-*ene* (**37**). To a stirred solution of 3 g (15.3 mmol) of alcohol (**4**) in 15 mL of pyridine was added portionwise 3.0 g (16.2 mmol) of toluene-p-sulfonyl chloride at room temperature under nitrogen. After being stirred for 1 h, 100 mL of water was added and extracted with benzene. Usual work-up afforded a crude tosylate (**6**) [NMR ($CDCl_3$) δ2.39 (3H, s, CH_3), 3.83 (4H, s, $-OCH_2CH_2O-$), 4.03 (2H, d, J = 7 Hz, CH_2OTs), 7.22 (2H, d, J = 8 Hz, ArH), 7.70 (2H, d, J = 8 Hz, ArH)] which was dissolved in 100 mL of dimethylformamide. To this stirred solution was added 1.6 g (15.5 mmol) of sodium bromide and heated at 80–85° for 2 h under nitrogen. Water (200 mL) was added to the reaction mixture, which was extracted with benzene. Usual work-up afforded a crude product which was chromatographed using chloroform as eluent to give 3.02 g (77%) of (**37**) as a colorless oil: NMR (CCl_4) δ3.28–3.54 (2H, m, CH_2–Br), 3.84 (4H, s, $-OCH_2CH_2O-$); MS *m/e*: 258 (M^+), 260 ($M^+ + 2$). (Found: C, 49.12; H, 5.67. Calc. for $C_{11}H_{15}O_2Br \cdot 0.1CHCl_3$: C, 49.18; H, 5.61%).

3,3 - (*Ethylenedioxy*) - 7 - *iodomethylbicyclo*[4.2.0]*octa* - 1(6) - *ene* (**8**). Alcohol (**5**) (3 g) (15.3 mmol) was treated with toluene-p-sulfonyl chloride (3 g) (16.2 mmol) in pyridine (15 mL) to give tosylate (**7**) which on reaction with sodium iodide (3 g) (20 mmol) in dimethylformamide afforded crude iodide (**8**) by following the same procedure described for the preparation of (**37**) mentioned above to give 3.7 g (80%) of iodide (**8**) as a colorless oil: NMR (CCl_4) δ3.3–3.55 (2H, m, CH_2I), 3.85 (4H, s, $-OCH_2CH_2O-$); MS *m/e* 306 (M^+).

4,4 - (*Ethylenedioxy*) - 7 - *toluene* - *p* - *sulfonylmethylbicyclo*[4.2.0]*octa* - 1(6) - *ene* (**10**). To a stirred solution of 1.35 g (3.86 mmol) of tosylate (**6**) in 10 mL of dimethylformamide was added 1.1 g (4.4 mmol) of sodium toluene-p-sulfinate, $4H_2O$ and 600 mg (4 mmol) of sodium iodide and the mixture was heated at 80–90° under nitrogen for 2 h. After addition of water, the reaction mixture was extracted with benzene. Usual work-up gave 1.15 g (90%) of sulfone (**10**) as a colorless oil: NMR ($CDCl_3$) δ2.45 (3H, s, CH_3), 3.93 (4H, s, $-OCH_2CH_2O-$), 7.32 (2H, d, J = 8 Hz, ArH), 7.76 (2H, d, J = 8 Hz, ArH). (Found: 334.1253 (M^+). $C_{18}H_{22}O_4S$ requires 334.1238).

3,3 - (*Ethylenedioxy*) - 7 - *toluene* - *p* - *sulfonylmethylbicyclo*[4.2.0]*octa* - 1(6) - *ene* (**11**). To a stirred solution of 3 g (9.8 mmol) of iodide (**8**) in 30 mL of dimethylformamide was added 2.53 g (10.1 mmol) of sodium toluene - p - sulfinate·$4H_2O$ and heated at 70–80° under nitrogen for 2 h. After addition of water, the reaction mixture was extracted with ethyl acetate. The extract was worked up as usual to afford a crude product which was crystallized from ethanol to give 2.8 g (85%) of sulfone (**11**) as colorless needles: m.p. 131–132°; NMR (CCl_4) δ2.41 (3H, s, CH_3), 3.1 (2H, broad s, CH_2SO_2Ts), 3.80 (4H, s, $-OCH_2CH_2O-$), 7.24 (2H, dJ = 8 Hz, ArH), 7.70 (2H, dJ = 8 Hz, ArH); MS *m/e* 334 (M^+). (Found: C, 64.72; H, 6.80. Calc. for $C_{18}H_{22}O_4S$: C, 64.65; H, 6.63%).

3,3 - (*Ethylenedioxy*) - 7 - *thiophenoxymethylbicyclo*[4.2.0]*octa* - 1(6) - *ene* (**9**). To a stirred solution of 600 mg (4.5 mmol) of sodium thiophenolate in 3 mL of anhydrous dimethylformamide was added dropwise a solution of 400 mg (1.3 mmol) of iodide (**8**) in 2 mL of dimethylformamide at 0° under nitrogen and stirred for 2 h. After quenching with saturated ammonium chloride solution, the reaction mixture was extracted with ethyl acetate. Usual work-up gave 370 mg (99%) of thiophenol ether (**9**) as a colorless oil: NMR (CCl_4) δ3.85 (4H, s, $-OCH_2CH_2O-$), 7.23 (5H, broad s, ArH); MS *m/e* 288 (M^+). (Found: C, 70.61; H, 7.00. Calc. for $C_{17}H_{20}O_2S$: C, 70.80; H, 6.99%).

3,3 - (*Ethylenedioxy*) - 7 - *benzenesulfoxymethylbicyclo*[4.2.0]*octa* - 1(6) - *ene* (**13**). To a stirred solution of 2.4 g (8.3 mmol) of thiophenol ether (**9**) in 40 mL of dichloromethane was added dropwise a solution of 2.0 g (11.6 mmol) of m-chloroperbenzoic acid in 20 mL of dichloromethane at −78° under nitrogen and stirred for 1 h. The dichloromethane layer was washed with 10% sodium hydroxide solution and worked up as usual to afford a gum which was chromatographed using ethyl acetate:dichloromethane (3:7 v/v) as eluent to give 2 g (80%) of sulfoxide (**13**) as a colorless oil: NMR (CCl_4) δ2.9 (2H, m, CH_2SOPh), 3.85 (4H, s, $-OCH_2CH_2O-$), 7.5 (5H, broad s, ArH); MS *m/e* 304 (M^+). (Found: C, 67.34; H, 6.62. Calc. for $C_{17}H_{20}O_3S$: C, 67.07; H, 6.62%).

3,3 - (*Ethylenedioxy*) - 7 - *benzenesulfonylmethylbicyclo*[4.2.0]*octa* - 1(6) - *ene* (**12**). To a stirred solution of 220 mg (0.72 mmol) of sulfoxide (**13**) in 10 mL of dichloromethane was added dropwise a solution of 175 mg (1.0 mmol) of m-chloroperbenzoic acid in 10 mL of dichloromethane at −20° under nitrogen and stirred for 1 h. The dichloromethane layer was worked up as usual to afford a crude product which was chromatographed using ethyl acetate:benzene (5 : 95 v/v) as eluent to give 150 mg (65%) of sulfone (**12**) as a colorless oil: NMR (CCl_4) δ 3.15 (2H, broad s, CH_2SO_2Ph), 3.83 (4H, s, $-OCH_2CH_2O-$) 7.4–8.0 (5H, m, ArH): MS *m/e* 320 (M^+). (Found: C, 63.55: H, 6.26. Calc. for $C_{17}H_{20}O_4S$: C, 63.72; H, 6.29%).

3,3 - (*Ethylenedioxy*) - 7 - [1 - (1 - *benzenesulfoxy*)*ethyl*]*bicyclo*[4.2.0]*octa* - 1(6) - *ene* (**15**). To a stirred solution of 150 mg (0.49 mmol) of sulfoxide (**13**) in 1 mL of anhydrous tetrahydrofuran was added 0.38 mL of 1.56 mol solution of n-BuLi in n-hexane at −78° under nitrogen. After being stirred for 10 min, 80 mg (0.56 mmol) of methyl iodide was added to the reaction mixture at −78° and stirring was continued for 10 min. Saturated ammonium chloride solution (5 mL) was added and the reaction mixture was extracted with ethyl acetate. Usual work-up afforded a crude product which was chromatographed using ethyl acetate:dichloromethane (1:9 v/v) as eluent to give 125 mg (80%) of sulfoxide (**15**) as a colorless oil: NMR (CCl_4) δ0.89, 0.93 (3H, each dJ = 7 Hz, CH_3), 3.87 (4H, s, $-OCH_2CH_2O-$), 7.48 (5H, m, ArH); MS *m/e* 318 (M^+). (Found: C, 67.63; H, 7.00. Calc. for $C_{18}H_{22}O_3S$: C, 67.89; H, 6.96%).

3,3 - (*Ethylenedioxy*) - 7 - [1 - (1 - *benzenesulfonyl*)*ethyl*]*bicyclo*[4.2.0] - *octa* - 1(6) - *ene* (**14**). Sulfone (**12**) (105 mg, 0.33 mmol) was treated with 56 mg (0.39 mmol) of methyl iodide by following the same procedure as described above to give 75 mg (68%) of sulfone (**14**) as a colorless oil: NMR (CCl_4) δ1.1, 1.2 (3H, each dJ = 7 Hz, CH_3), 3.86 (4H, s, $-OCH_2CH_2O-$), 7.4–7.95 (5H, m, ArH); MS *m/e* 334 (M^+). (Found: C, 64.80; H, 6.75. Calc. for $C_{18}H_{22}O_4S$: C, 64.64; H, 6.63%.)

3,3 - (*Ethylenedioxy*) - 7 - [1 - (1 - *benzenesulfinyl*)*isopropyl*]*bicyclo*[4.2.0]*octa* - 1(6) - *ene* (**17**). Sulfoxide (**13**) (200 mg, 0.66 mmol) was treated with 2.2 eq. of methyl iodide and 2.2 eq. of n-BuLi as described for compound (**15**) to give 190 mg (88%) of sulfoxide (**17**) as a colorless oil: NMR (CCl_4) δ0.93, 0.96 (3H, each s, $CH_3 \times 2$), 3.86 (4H, s, $-OCH_2CH_2O-$), 7.48 (5H, broad s, ArH); MS *m/e* 332 (M^+). (Found: C, 68.92; H, 7.18. Calc. for $C_{19}H_{24}O_3S$: C, 68.64; H, 7.28%.)

3,3 - (*Ethylenedioxy*) - 7 - [1 - (1 - *benzenesulfonyl*)*isopropyl*]*bicyclo*[4.2.0]*octa* - 1(6) - *ene* (**16**). Sulfone (**12**) (110 mg, 0.34 mmol) was methylated by following the same procedure as described for compound (**17**) to give 108 mg (91%) of sulfone (**16**) as a colorless oil: NMR (CCl_4) δ1.1, 1.2 (3H, each s, $CH_3 \times 2$), 3.85 (4H, s, $-OCH_2CH_2O-$), 7.38–7.96 (5H, m, ArH); MS *m/e* 348 (M^+). (Found: C, 65.64; H, 7.20. Calc. for $C_{19}H_{24}O_4S$: C, 65.50; H, 6.94%).

Ring-opening reactions

Compound (**10**) (*Entry No.* 1 *in Table* 1). To a stirred solution of 500 mg (1.5 mmol) of sulfone (**10**) in 7 mL of THF was added 1.2 mL of 1.5 mol solution of n-BuLi solution in n-hexane under nitrogen at −78°. After the reaction temperature was raised to −30°, stirring was continued for 10 min at the same temperature. After usual work-up by using benzene for extraction, the crude product was chromatographed using dichloromethane as eluent to give 287 mg (58%) of diene (**18**) as a colorless oil: NMR ($CDCl_3$) δ2.44 (3H, s, CH_3), 3.88(4H, s, $-OCH_2CH_2O-$), 4.73 (1H, broad s, olefinic proton), 4.90 (1H, broad s, olefinic proton), 5.47 (1H, tJ = 9 Hz, olefinic proton), 7.28 (2H, dJ = 8 Hz, ArH), 7.72 (2H, dJ = 8 Hz, ArH); (Found: 334.1222 (M^+). $C_{18}H_{22}O_4S$ requires 334.1237).

Compound (**11**) (*Entry No.* 2 *in Table* 1). Sulfone (**11**) (167 mg, 0.5 mmol) was subjected to the same reaction conditions described for compound (**10**) to give 150 mg (90%) of diene (**19**) as a colorless oil after chromatography using benzene as eluent: UV (EtOH) (log ϵ) 238 nm (3.94); NMR (CCl_4) δ2.45 (3H, s, $ArCH_3$), 3.71 (2H, d, J = 8 Hz, CH_2SO_2Ts), 3.83 (4H, s, $-OCH_2CH_2O-$), 4.6 (1H, broad s, olefinic proton), 4.86 (1H, broad s, olefinic proton), 5.4 (1H, distorted t J = 8 Hz, olefinic proton), 7.25 (2H, dJ = 8 Hz, ArH), 7.66 (2H, dJ = 8 Hz, ArH); MS *m/e* 344 (M^+). (Found: C, 64.90; H, 6.82. Calc. for $C_{18}H_{22}O_4S$: C, 64.65; H, 6.63%).

Compound (**12**) (*Entry No.* 3 *in Table* 1). Sulfone (**12**) (160 mg, 0.5 mmol) was subjected to the same reaction conditions as described for compound (**10**) to give 147 mg (92%) of diene (**20**) as a colorless oil after chromatography using benzene as eluent: UV (EtOH) (log ϵ) 237 nm (3.93); NMR (CCl_4) δ3.76 (2H, d, J = 8 Hz, CH_2SO_2Ph), 3.84 (4H, s, $-OCH_2CH_2O-$), 4.66 (1H, broad s, olefinic proton), 4.90 (1H, broad s, olefinic proton), 5.10 (1H, distorted tJ = 8 Hz, olefinic proton), 7.40–8.0 (5H, m, ArH); MS *m/e* 320 (M^+). (Found: C, 63.62; H, 6.35. Calc. for $C_{17}H_{20}O_4S$: C, 63.72; H, 6.29%).

Compound (**13**) (*Entry No.* 4 *in Table* 1). Sulfoxide (**13**) (152 mg, 0.5 mmol) was subjected to the same reaction conditions as described for compound (**10**) to give a crude gum which was chromatographed on 5 g of silica gel using ethyl acetate:dichloromethane (5:95 v/v) as eluent to give 76 mg (50%) of sulfoxide (**21**) as a colorless oil: UV (EtOH) (log ϵ) 243 nm (4.20); NMR (CCl_4) δ3.4 (1H, dJ = 12 Hz, CHSOPh), 3.85 (4H, s, $-OCH_2CH_2O-$), 4.8 (1H, dJ = 10 Hz, olefinic proton), 5.03 (1H, dJ = 16 Hz, olefinic proton), 6.27 (1H, dd$J$ = 10 and 16 Hz, olefinic proton), 7.43 (5H, broad s, ArH); MS *m/e* 304 (M^+). (Found: C, 66.90; H, 6.55. Calc. for $C_{17}H_{20}O_3S$: C, 67.07; H, 6.62%).

Further elution with ethyl acetate:dichloromethane (1:9 v/v) as eluent gave 66.7 mg (47%) of sulfoxide (**22**) as a colorless oil: UV (EtOH) (log ϵ) 235 nm (4.06); NMR (CCl_4) δ3.38 (2H, dJ = 9 Hz, CH_2SOPh), 3.9 (4H, s, $-OCH_2CH_2O-$), 4.63 (1H, broad s, olefinic proton), 4.93 (1H, broad s, olefinic proton), 5.52 (1H, tJ = 9 Hz, olefinic proton); MS *m/e* 284 (M^+). (Found: C, 63.60; H, 8.72. Calc. for $C_{15}H_{24}O_3S$: C, 63.34; H, 8.51%).

Compound (**14**) (*Entry No.* 5 *in Table* 1). Sulfone (**14**) (55 mg, 0.17 mmol) was subjected to the same reaction conditions as described for compound (**10**) to give 10 mg (31%) of diene (**23**) as a colorless oil after chromatography using benzene as eluent: UV

(EtOH) (log ε) 240 nm (3.97); NMR (CCl_4) δ1.46 (3H, dJ = 7 Hz, CH_3), 3.0–3.4 (1H, m, $CHSO_2Ph$), 3.87 (4H, s, $-OCH_2CH_2O-$), 4.67 (1H, broad s, olefinic proton), 4.94 (1H, broad s, olefinic proton), 5.25 (1H, dJ = 10 Hz, olefinic proton), 7.5–8.0 (5H, m, ArH); MS *m/e* 334 (M^-). (Found: C, 64.72; H, 6.60. Calc. for $C_{18}H_{22}O_4S$: C, 64.64; H, 6.63%).

Sulfoxide (**13**) was also treated with lithium diisopropylamide instead of n-BuLi under the same reaction conditions described for compound (**10**) to give compound (**21**) (75%) after chromatography using benzene as eluent as a single product.

Compound (**15**) (*Entry No. 6 in Table 1*). Sulfoxide (**15**) (53 mg, 0.17 mmol) was subjected to the same reaction conditions as described for compound (**10**) to give 37 mg (70%) of diene (**24**) as a colorless oil after chromatography using ethyl acetate:dichloromethane (5:95 v/v) as eluent: UV (EtOH) (log ε) 253 nm (4.09); NMR (CCl_4) δ1.64 (3H, dJ = 5 Hz, CH_3), 3.4(1H, dJ = 12 Hz, CHSOPh), 3.67 (1H, dJ = 12 Hz, CHSOPh), 3.86 (4H, s, $-OCH_2CH_2O-$), 5.56 (1H, m, olefinic proton), 5.92 (1H, dJ = 14 Hz, olefinic proton), 7.3–7.6 (5H, m, ArH); MS *m/e* 318 (M^+). (Found: C, 68.10; H, 7.11. Calc. for $C_{18}H_{22}O_3S$: C, 67.89; H, 6.96%).

Isomerization of diene (**22**). A solution of 10 mg (0.04 mmol) of diene (**22**) in 1 mL of carbon tetrachloride was stored for 2 days at room temperature. Evaporation of the solvent afforded a crude product which was chromatographed using ethyl acetate:dichloromethane (1:9 v/v) as eluent to give 9.8 mg (98%) of (**31**) as a colorless oil: UV (EtOH) (log ε) 246 nm (4.17); NMR (CCl_4) δ3.5 (2H, broad s, CH_2SO^nBu), 3.9 (4H, s, $-OCH_2CH_2O-$), 5.05 (1H, dJ = 11 Hz, olefinic proton), 5.2 (1H, dJ = 16 Hz, olefinic proton), 6.68 (1H, dd$J$ = 11 and 16 Hz, olefinic proton); MS *m/e* 284 (M^+). (Found: C, 63.43; H, 8.66. Calc. for $C_{15}H_{24}O_3S$: C, 63.34; H, 8.51%).

Hydrolysis of diene (**19**). To a stirred solution of 111 mg (0.33 mmol) of diene (**19**) in 2 mL of methanol was added 0.2 mL of 10% hydrochloric acid at room temperature and stirred for 2 h. After addition of water, the reaction mixture was extracted with dichloromethane. Usual work-up of the extract gave 89 mg (92%) of enone (**25**) as a colorless oil: IR ($CHCl_3$) 1665 cm^{-1}; NMR (CCl_4) δ2.03 (3H, s, CH_3), 2.43 (3H, s, $ArCH_3$), 3.88 (2H, dJ = 8 Hz, CH_2SO_2Ts), 5.73 (1H, s, olefinic proton), 5.85 (1H, distorted tJ = 8 Hz, olefinic proton), 7.26 (2H, dJ = 8 Hz, ArH), 7.7 (2H, dJ = 8 Hz, ArH); MS *m/e* 290 (M^+). (Found: C, 66.32; H, 6.42. Calc. for $C_{16}H_{18}O_3S$: C, 66.19; H, 6.25%).

Reaction of sulfone (**10**) *with cyclohexanone.* To a stirred solution of 334 mg (1 mmol) of sulfone (**10**) in 3 mL of THF was added 1 mL of 1.5 mol solution of n-BuLi in hexane at −78° under nitrogen. After being stirred for 10 min, a solution of 100 mg (1.02 mmol) of cyclohexanone in 1 mL of THF was added to the reaction mixture at −78° and the stirring was continued for 1 h at −78°. Extraction with benzene, followed by chromatography of the resulting crude product using dichloromethane as eluent gave 224 mg (52%) of (**32**) as a colorless oil: IR ($CHCl_3$) 3580 cm^{-1}; NMR ($CDCl_3$) δ2.46 (3H, s, CH_3), 3.94 (4H, s, $-OCH_2CH_2O-$), 7.28 (2H, dJ = 8 Hz, ArH), 7.77 (2H, dJ = 8 Hz, ArH); (Found: 432.1957 (M^+). $C_{24}H_{32}O_5S$ requires 432.1968).

Reaction of diene (**18**) *with cyclohexanone.* To a stirred solution of 350 mg (1.05 mmol) of diene (**18**) in 15 mL of THF was added 1 mL of 1.5 mol solution of n-BuLi in hexane at −78° under nitrogen. After being stirred for 10 min at −78°, a solution of 103 mg (1.05 mmol) of cyclohexanone in 1 mL of THF was added and the reaction mixture was stirred for 1 h. After addition of water, the mixture was extracted with benzene. The organic layer was worked up as usual to afford a crude product which was chromatographed using dichloromethane as eluent to give 128 mg (29%) of (**34**) as a colorless oil: IR ($CHCl_3$) 3580 cm^{-1}; NMR (CCl_4) δ2.43 (3H, s, CH_3) 3.72 (4H, s, $-OCH_2CH_2O-$), 4.68 (1H, broad s, olefinic proton), 4.86 (1H, broad s, olefinic proton), 5.52 (1H, dJ = 12 Hz, olefinic proton), 7.22 (2H, dJ = 8 Hz, ArH), 7.60 (2H, dJ = 8 Hz, ArH). (Found: 432.1999(M^+). $C_{24}H_{34}O_5S$ requires 432.1971).

4,4 - (*Ethylenedioxy*) - 7 - *diphenylphosphinoylmethylbicyclo*[4.2.0]*octa* - 1(**6**) - *ene* (**38**). To a stirred solution of 259 mg (1 mmol) of bromide (**37**) in 10 mL of THF was added dropwise 1.2 mL of 1 mol solution of lithium diphenylphosphide (prepared from 4 atm of lithium and chlorodiphenylphosphine) in THF at −20° and stirred for 10 min. After quenching with saturated ammonium chloride solution, the reaction mixture was extracted with benzene. Usual work-up of the extract afforded a crude product which was dissolved in 20 mL of chloroform. To this stirred solution was added 5 mL of 5% hydrogen peroxide solution at room temperature and stirred for 30 min. A crude product resulted from usual work-up of this organic layer was chromatographed using chloroform as eluent to give 323 mg (85%) of (**38**) as a colorless oil: NMR (CCl_4) δ3.82 (4H, s, $-OCH_2CH_2O-$), 7.27–8.00 (10H, m, ArH × 2); MS *m/e* 380 (M^+); (Found: C, 60.67; H, 5.45. Calc. for $C_{23}H_{25}O_3P{\cdot}2.6CHCl_3$: C, 60.71, H, 5.49%).

4 - *Hydroxy* - 7 - *toluene* - *p* - *sulfonyloxymethylbicyclo*[4.2.0]*octa* - 1(6) - *ene* (**39**). To a stirred solution of 9.3 g (56 mmol) of alcohol (**2**) in 150 mL of THF, 1 L of liquid ammonia and 2 mL of anhydrous ethanol was added 3.0 g (130 mmol) of sodium at −78° and stirred for 1 h. Extraction with benzene, followed by usual work-up afforded a crude gum which was dissoved in 100 mL of pyridine. To this solution was added 12 g (64.7 mmol) of toluene-p-sulfonyl chloride under nitrogen and stirred for 2 h at room temperature to give a gum, after usual work-up of benzene extract, which was dissolved in 100 mL of acetone and 10% HCl (5 mL) was added to this solution under stirring. After being stirred for 20 min, water was added and the reaction mixture was extracted with chloroform. The organic layer was treated as usual to afford a crude product which was dissolved in 100 mL of methanol. To this stirred solution was added 3 g (79 mmol) of sodium borohydride at 0°. The residue, resulted from the evaporation of the solvent, was extracted with benzene. Evaporation of the solvent gave a crude tosylate which was chromatographed using benzene as eluent to give 16.0 g (98%) of (**39**) as a colorless oil: IR ($CHCl_3$) 3600 (OH) cm^{-1}; NMR ($CDCl_3$) δ2.40 (3H, s, CH_3), 4.06 (2H, dJ = 7 Hz, CH_2–OTs), 7.30 (2H, dJ = 8 Hz, ArH), 7.73 (2H, dJ = 8 Hz, ArH).

4 - *Benzoyloxy* - 7 - *bromomethylbicyclo*[4.2.0]*octa* - 1(6) - *ene* (**40**). To a stirred solution of 16.0 g (55 mmol) of (**39**) in 100 mL of pyridine was added 7.8 g (55.5 mmol) of benzoyl chloride at room temperature under nitrogen and stirred for 1 h. To a solution of crude product, which was obtained by usual work-up of benzene extract, in 100 mL of dimethylformamide was added 5.3 g (51.5 mmol) of sodium bromide under nitrogen and heated at 80–85° for 2 h. After extraction with benzene, organic layer was worked up as usual to afford a crude gum which was chromatographed using benzene as eluent to give 13.2 g (55%) of (**40**) as a colorless oil: NMR ($CDCl_3$) δ3.34–3.63 (2H, m, CH_2Br), 5.00–5.50 (1H, m, $\rangle CH-O$), 7.25–7.60 (3H, m, ArH), 7.85–8.18 (2H, m, ArH); MS *m/e*: 302 (M^+), 304 ($M^+ + 2$).

4 - *Benzoyloxy* - 7 - *diphenylphosphinoylmethylbicyclo*[4.2.0]*octa* - 1(6) - *ene* (**41**). To a stirred solution of 3.5 g (11.6 mmol) of (**40**) in 70 mL of THF was added 1.5 mL of 1 mol solution of lithium diphenylphosphide (prepared from 4 atm of lithium and chlorodiphenylphosphine) in THF at −20° under nitrogen. After being stirred for 16 h at room temperature, saturated ammonium chloride solution (50 mL) was added and the reaction mixture was extracted with benzene. A crude product was dissolved in 100 mL of chloroform. To this solution was added 10 mL of 5% hydrogen peroxide solution at room temperature and stirred for 1 h. The organic layer was worked up as usual to afford a brown gum which was chromatographed using chloroform as eluent to give 4.7 g (92%) of (**41**) as a colorless oil: NMR ($CDCl_3$) δ4.90–5.46 (1H, m, $\rangle CH-O-$), 7.00–8.10 (15H, m, ArH); MS *m/e*: 442 (M^+).

4 - *Hydroxy* - 7 - *diphenylphosphinoylmethylbicyclo*[4.2.0]*octa*-1(6) - *ene* (**42**). To a stirred solution of 2 g (4.53 mmol) of (**41**) in 20 mL of methanol was added 5 mL of 10% sodium hydroxide solution at room temperature and stirred for 8 h. Extraction with benzene, followed by usual work-up afforded a crude alcohol which was chromatographed using chloroform as eluent to give 1.17 g (72%) of (**42**) as a colorless oil: IR ($CHCl_3$) 3600 (OH) cm^{-1}; NMR ($CDCl_3$) δ3.55–4.10 (1H, m, $\rangle CH-OH$), 7.23–8.00 (10H, m, ArH); MS *m/e*: 338 (M^+).

4 - [1 - (1 - *Ethoxy*)*ethoxy*] - 7 - *diphenylphosphinoylmethyl-*

bicyclo[4.2.0]*octa* - 1(6) - *ene* (**43**). To a stirred solution of 1.6 g (4.73 mmol) of (**42**) in 30 mL of dichloromethane was added 720 mg (10 mmol) of ethyl vinyl ether and a catalytic amount of toluene - p - sulfonic acid under nitrogen at room temperature and stirred for 1 h. Usual work-up of organic layer afforded a crude gum which was chromatographed using chloroform as eluent to give 880 mg (46%) of (**43**) as a colorless oil: NMR ($CDCl_3$) δ1.18 (3H, tJ = 8 Hz, CH_3), 1.23 (3H, dJ = 5 Hz, CH_3), 4.55–4.90 (1H, m, –O–CH–O–), 7.30–8.00 (10H, m, ArH); MS *m/e*: 318 ($M^+ - 29$).

Ring-opening reaction

Compound (**38**) (*Entry No.* 1 *in Table* 2). To a stirred solution of 81 mg (0.213 mmol) of phosphine oxide (**38**) in 5 mL of THF was added 1 mL of 1.5 mol solution of lithium diisopropylamide in THF at −78° under nitrogen. After being stirred for 15 min at −78°, stirring was continued for 16 h at −20°. Usual treatment of benzene extract afforded a crude gum which was chromatographed using chloroform as eluent to give 61 mg (76%) of (**44**) as a colorless oil: NMR (CCl_4) δ2.87–3.24 (EH, m, CH_2–P–), 3.85 (4H, s, –OCH_2CH_2O–), 4.58 (1H, broad s, olefinic proton), 4.73 (1H, broad s, olefinic proton), 5.30–5.80 (1H, m, olefinic proton), 7.65–7.97 (10H, m, ArH); MS *m/e*: 380 (M^+). (Found: C, 59.37; H, 5.48. Calc. for $C_{23}H_{25}O_3P \cdot 3CHCl_3$: C, 59.38; H, 5.37%).

Compound (41) (*Entry No.* 2 *in Table* 2). By following the same procedure described for compound (**38**), compound (**41**) (450 mg) was converted into compound (**45**) (92 mg, 27%) as a colorless oil after chromatography using chloroform as eluent: IR ($CHCl_3$) 3600 (OH) cm^{-1}; NMR ($CDCl_3$) δ4.00–4.30 (1H, m, >CH–OH), 4.56 (1H, broad s, olefinic proton), 4.69 (1H, broad s, olefinic proton), 5.05–5.50 (1H, m, olefinic proton), 7.30–8.00 (10H, m, ArH); MS *m/e*: 338 (M^+).

Compound (**42**) (*Entry No.* 3 *in Table* 2). To a stirred solution of 169 mg (0.5 mmol) of compound (**42**) in 5 mL of THF was added 0.5 mL of 1.5 mol solution of n-BuLi in hexane at −78° under nitrogen. After being stirred for 16 h at −20°, saturated ammonium chloride solution (10 mL) was added. Usual work-up of benzene extract gave a crude gum which was chromatographed using chloroform as eluent to give 72 mg (43%) of (**45**) as a colorless oil. This was identical with the sample obtained above.

Compound (**43**) (*Entry No.* 4 *in Table* 2). By following exactly the same procedure for compound (**38**), compound (**43**) (880 mg) afforded compound (**46**) (115 mg, 13%) after chromatography using chloroform as eluent: NMR ($CDCl_3$) δ1.17 (3H, tJ = 8 Hz, CH_3), 1.26 (3H, dJ = 5 Hz, CH_3), 4.56 (1H, broad s, olefinic proton), 4.72 (1H, broad s, olefinic proton), 5.33–5.80 (1H, m, olefinic proton), 7.25–8.00 (10H, m, ArH); MS *m/e*: 410 (M^+).

(E) - 1 - (2 - *Cyclohexylidene* - *ethylidene*) - 5,5 - (*ethylenedioxy*) - 2 - *methylenecyclohexane* (**47**).

(i) *From compound* (**44**) *and cyclohexanone.* To a stirred solution of 120 mg (0.316 mmol) of phosphine oxide (**44**) in 8 mL of THF was added 0.25 mL of 1.5 mol solution of n-BuLi in hexane at −78°. After being stirred for 30 min at −78°, a solution of 31 mg (0.316 mmol) of cyclohexanone in 2 mL of THF was added at −78°. Stirring was continued for 1.5 h at −20°, and then for 1.5 h at room temperature. Removal of the solvent from benzene extract afforded a crude product which was chromatographed using benzene as eluent to give 28 mg (35%) of (**47**) as a colorless oil: NMR (CCl_4) δ3.73 (4H, s, –OCH_2CH_2O–), 4.66 (1H, broad s, olefinic proton), 4.91 (1H, broad s, olefinic proton), 5.82 (1H, dJ = 12 Hz, olefinic proton), 6.32 (1H, dJ = 12 Hz, olefinic proton); MS *m/e*: 260 (M^+). [Found: 260.1760 (M^+). $C_{17}H_{24}O_2$ requires 260.1775).

(ii) *From compound* (**38**) *and cyclohexanone.* To a stirred solution of 190 mg (0.5 mmol) of phosphine oxide (**38**) in THF was added 0.5 mL of 1.5 mol solution of lithium diisopropylamide in THF at −78° under nitrogen. After being stirred for 16 h at −20°, a solution of cyclohexanone (51 mg, 0.52 mmol) in 3 mL of THF was added to the reaction mixture at −78°. Stirring was continued for 1.5 h at −20°, and then for 1.5 h at room temperature. Evaporation of the solvent from benzene extract afforded a crude product which was chromatographed on 5 g of silica gel using benzene as eluent to give 44 mg (34%) of (**47**) as a colorless oil, which was identical to (**47**) obtained above.

(*E*) - 1 - [2 - (2 - *methylcyclohexylidene*)*ethylidene*] - 5,5 - *ethylenedioxy* - 2 - *methylenecyclohexane* (**48**). (**48**) was obtained from (**44**) and (**38**) with 2-methylcyclohexanone in 20 and 5% yields respectively, in the same manner as for the compound (**47**) as a colorless oil: NMR (CCl_4) δ1.10 (3H, dJ = 7 Hz, CH_3), 3.83 (4H, s, –OCH_2CH_2O–), 4.63 (1H, broad s, olefinic proton), 4.90 (1H, broad s, olefinic proton), 5.82 (1H, dJ = 12 Hz, olefinic proton), 6.35 (1H, dJ = 12 Hz, olefinic proton); MS *m/e*: 274 (M^+). (Found: 274.1928 (M^+). $C_{18}H_{26}O_2$ requires 274.1931).

5 - (*E*) - 3,3 - *ethylenedioxy* - *vitamin* D_3 (**50**). To a stirred solution of 242 mg (0.637 mmol) of phosphine oxide (**44**) was added 0.5 mL of 1.5 mol solution of lithium diisopropylamide in THF at −78° under nitrogen. After being stirred for 30 min, a solution of ketone (**49**) (84 mg, 0.318 mmol) in 5 mL of THF was added at −78°. Stirring was continued for 14 h at −20°, and then for 1.5 h at room temperature. Usual work-up of benzene extract afforded a crude product which was chromatographed using n-hexane : chloroform (10:1 v/v) as eluent to give 39 mg (29%) of (**50**) as a colorless oil: NMR (CCl_4) δ0.58 (3H, s, CH_3), 0.87 (9H, dJ = 6 Hz, $CH_3 \times 3$), 3.87 (4H, s, –OCH_2CH_2O–), 4.6 (1H, broad s, olefinic proton), 4.9 (1H, broad s, olefinic proton), 5.67 (1H, dJ = 12 Hz, olefinic proton), 6.36 (1H, dJ = 12 Hz, olefinic proton); MS *m/e*; 426 (M^+); UV (hexane) (log ϵ) 272 (3.97). (Found: C, 69.01; H, 9.28. Calc. for $C_{29}H_{46}O_2 \cdot 0.75CHCl_3$; C, 69.22; H, 9.13%).

Sulfur dioxide adduct (**52**). To a solution of 900 mg (2.113 mmol) of (**50**) in 20 mL of benzene was added 10 mL of 6% sulfurous acid solution and stirred vigorously for 2 h at room temperature. Benzene layer was treated as usual to afford a crude product which was chromatographed using chloroform as eluent to give 975 mg (95%) of (**52**) as a colorless oil: NMR (CCl_4) δ0.58, 0.68 (each s, CH_3), 0.87 (9H, dJ = 5 Hz, $CH_3 \times 3$), 3.55 (2H, broad s, –CH_2SO_2), 3.87 (4H, s, –OCH_2CH_2O–), 4.25–4.90 (3H, m, >CH–SO_2 and olefinic proton); MS *m/e*: 426 ($M^+ - 64$). (Found: C, 56.94; H, 7.68. Calc. for $C_{29}H_{46}O_4S \cdot 1.2CHCl_3$: C, 57.21; H, 7.51%).

Sulfur dioxide adduct (**53**). To a stirred solution of 935 mg (1.91 mmol) of ketal (**52**) in 20 mL of acetone was added 1 mL of trifluoroacetic acid and 2 mL of 10% hydrochloric acid solution at room temperature and stirred for 12 h. This benzene layer was worked up as usual to afford a crude product which was chromatographed using chloroform as eluent to give 640 mg (76%) of (**53**) as a colorless oil: IR ($CHCl_3$) 1700 (C=O) cm^{-1}; NMR ($CDCl_3$) δ0.54, 0.63 (each s, CH_3), 0.85 (9H, dJ = 6 Hz, $CH_3 \times 3$), 3.75 (2H, broad s, –CH_2SO_2), 4.66 (2H, broad s, CH–SO_2 and olefinic proton); MS *m/e*: 382 ($M^+ - 64$). (Found: C, 60.60; H, 7.92. Calc. for $C_{27}H_{42}O_3S \cdot 0.9CHCl_3$: C, 60.48; H, 7.80%).

Sulfur dioxide adduct (**54**). To a stirred solution of 395 mg (0.886 mmol) of ketone (**53**) in 5 mL of chloroform and 5 mL of methanol was added 50 mg (1.32 mmol) of sodium borohydride at 0° and stirring was continued for 1 h at 0°. After evaporation of the solvent, water was added and the reaction mixture was extracted with benzene. Benzene layer was treated as usual to afford a crude product which was chromatographed using chloroform as eluent to give 335 mg (85%) of (**54**) as a colorless oil: IR ($CHCl_3$) 3600 (OH) cm^{-1}; NMR ($CDCl_3$) δ0.56, 0.64 (each s, CH_3), 0.86 (9H, dJ = 5 Hz, $CH_3 \times 3$), 3.63 (2H, broad s, –CH_2SO_2), 3.85–4.20 (1H, m, >CH–OH), 4.67 (2H, broad s, >CH–SO_2 and olefinic proton); MS *m/e*: 384 ($M^+ - 64$). (Found: C, 68.22; H, 9.36. Calc. for $C_{27}H_{44}O_3S \cdot 0.25CHCl_3$: C, 68.40; H, 9.32%).

5(E)-vitamin D_3 (**55**). To a solution of 200 mg (0.446 mmol) of (**54**) in 10 mL of ethanol was added 200 mg of sodium bicarbonate and the resulting mixture was refluxed for 30 min under nitrogen. After evaporation of the solvent, water was added and the mixture was extracted with benzene. Usual work-up afforded a crude product which was chromatographed using benzene as eluent to give 135 mg (79%) of (**55**) as a colorless powder: m.p. 87–91° (acetone); UV (hexane) (log ϵ) 270 (4.46); IR ($CHCl_3$) 3600 (OH) cm^{-1}; NMR ($CDCl_3$) δ0.57 (3H, s, CH_3), 0.87 (9H, dJ = 6 Hz, $CH_3 \times 3$), 3.67 – 4.20 (1H, m, $\rangle$CH–OH), 4.69 (1H, broad s, olefinic proton), 4.96 (1H, broad s, olefinic proton), 5.86 (1H, dJ = 6 Hz, olefinic proton), 6.56 (1H, dJ = 6 Hz, olefinic proton); MS *m/e*: 384 (M^+). $[\alpha]_D$ + 115.4° (c = 0.37).

5(E) - vitamin D_3 (**55**) *from sulfur dioxide adduct* (**56**) *of vitamin D_3*. To a stirred solution of 200 mg (0.446 mmol) of sulfur dioxide adduct (**56**) in 10 mL of ethanol was added 200 mg of sodium bicarbonate and the resulting mixture was refluxed for 20 min and followed by the same procedure as above to give 135 mg (79%) of 5(E)-vitamin D_3 (**55**) as colorless needle: m.p. 87–89° (acetone); $[\alpha]_D$ + 120.6° (c = 0.345) which was identical to (**55**) obtained above.

Note added in proof: After submission of this paper, a total synthesis of 1α, 25-dihydroxycholecalciferol has been reported by E. G. Baggiolini *et al. J. Am. Chem. Soc.* **104**, 2945 (1982).

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[16]Under these conditions only *trans*-vitamin D_3 was obtained and we could not detect any signals due to vitamin D_3 in the NMR spectrum of crude reaction product. This should be compared with the reported results [15b] in which 1:1 mixture of vitamin D_3 and *trans*-vitamin D_3 was obtained.

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