Stereocontrolled Synthesis of (+)-Isocalamendiol via Photocycloaddition

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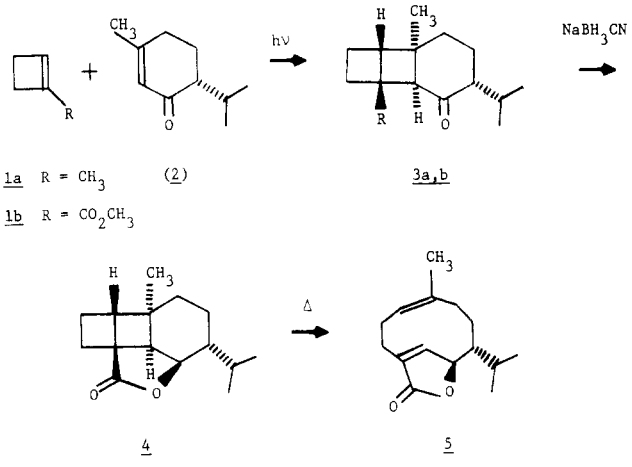
Photocycloaddition of methyl cyclobutenecarboxylate (**1b**) to (−)-piperitone (**2**) affords the photoadduct **3b**. Sodium cyanoborohydride reduction of **3b** affords the lactone **4** which upon thermolysis yields the *cis*-1(10)-*trans*-4-germacrene **5**. Flash vacuum pyrolysis of **3b** affords the *trans*-1(10)-*cis*-4-germacrene **6b** together with three elemane ketones **8b**, **9b**, and **10b**. Thermolysis of **3b** at 210 °C for 3 h affords the cadinane **7b** via the intermediate *trans*-1(10)-*cis*-4-germacrene **6b**. The cadinane **7b** has been converted into (+)-isocalamendiol (**14b**) by using an MEM ether to protect the C-6 hydroxyl group.

Previous work in our laboratory has shown that the isoprene synthon methylcyclobutene (**1a**) can be used to convert terpenes to a series of sesquiterpenes via a photocycloaddition–thermolysis reaction sequence.[1] This was found to give ready access to both elemane, germacrane, and cadinane sesquiterpenes and was potentially capable of yielding several other isomeric sesquiterpene systems. However, when methylcyclobutene (**1a**) was used, there was no functionality incipient in the isoprene synthon whereas many sesquiterpenes are functionalized at carbon 15.[2] Our previous work using dimethyl cyclobutenedicarboxylate in model systems and in the synthesis of 1,4-cyclosteroids suggested the use of methyl cyclobutenecarboxylate (**1b**) as an ideal functionalized isoprene synthon.[3] It was also readily available and relatively stable to photolysis conditions, undergoing photocycloaddition over both dimerization and polymerization.[4] Concurrent with this work Lange et al.,[5] Wender et al.,[6] and Wilson et al.[7] have also shown the usefulness of this reagent as well as the conversion of the tricyclo[4.4.0.0^{2,5}]decane intermediate **3b** to a number of sesquiterpene systems. Detailed below is our work utilizing methyl cyclobutenecarboxylate (**1b**) as an isoprene synthon for the synthesis of the *cis*-1(10)-*trans*-4-germacranolide **5** and the *trans*-1(10)-*cis*-4-germacrene **6b** as well as the first stereocontrolled synthesis of the cadinane sesquiterpene (+)-isocalamendiol (**14b**).[8]

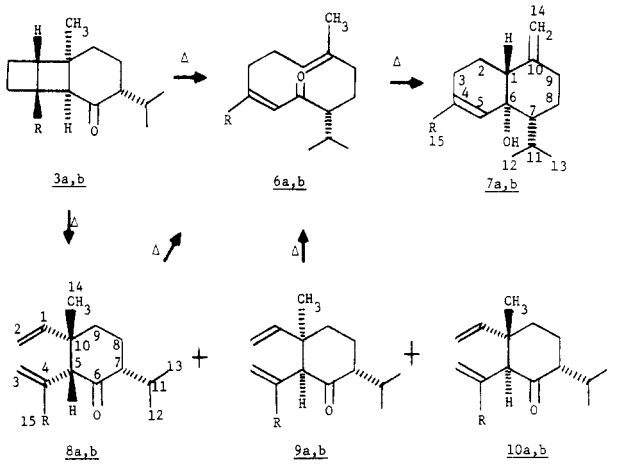
Results and Discussion

Photocycloaddition of methyl cyclobutenecarboxylate (**1b**) and (−)-piperitone (**2**) [$[\alpha]_D$ −30.5° (*c* 0.339 g/mL), 61% ee] gave the tricyclo[4.4.0.0^{2,5}]decane photoadduct **3b** in 75% isolated yield after chromatography[5b,6b-d,7] (Scheme I). Reaction occurred at temperatures ranging from 0 to −78 °C; however, lower reaction temperatures facilitated higher yields of product. Recrystallization of the purified photoadduct gave fine crystals (mp 57–58 °C, $[\Theta]_{310}$ +9250) which were shown to be enantiomerically pure by utilizing a chiral shift reagent study.[9] The structure of **3b** was determined by a comparison of its proton NMR spectra with those of similar systems,[1] and its absolute stereochemistry was derived from its circular dichroism spectrum as well as by knowledge of the absolute stereochemistry of (−)-piperitone (**2**).[10] In addition to this data, **3b** has previously been converted to (±)-10-epijunenol[6b] as well

Scheme I



Scheme II[a]



[a] a R = CH_3; b R = CO_2CH_3.

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Table I. Carbon-13 NMR Spectral Data of Elemane Thermal Products

carbon	compd 8b	9b	10b
1	140.3	141.0	133.6
2	114.8	114.6	118.9
3	129.9	130.2	124.0
4	132.6	132.6	146.5
5	59.6	57.6	63.5
6	208.5	211.1	210.8
7	56.0	56.3	52.2
8	25.2	24.2	23.2
9	41.1	36.6	31.3
10	47.0	46.6	44.3
11	26.3	28.3	25.9
12	21.1	20.7	20.9
13	18.5	20.6	18.5
14	25.2	25.4	24.0
15	168.0	168.0	166.9
OMe	51.9	52.0	51.4

as being converted now into (+)-isocalamendiol (**14b**).

Reduction of **3b** using $NaBH_3CN$[11] gave the lactone **4** in 46% isolated yield.[5b,7] Thermolysis of **4** afforded the *cis*-1(10)-*trans*-4-germacranolide **5**,[5b,7] whose structure was determined by comparison of its spectral data with those of isoaristolactone and aristolactone.[12]

Thermolysis of the ester **3b** under a variety of conditions gave results analogous to those observed for the methyl system **3a**.[1b] Flash vacuum pyrolysis of the photoadduct **3b** at 500 °C afforded the *trans*-1(10)-*cis*-4-germacrene **6b** (19% yield) as well as the three elemane ketones, **8b**, **9b**, and **10b** (27%, ratio of 49:43:8), and the *trans*-decalin **7b** (13%) (see Scheme II). The structure of **6b** was determined by spectral analysis as well as comparison to the spectral data of the known *trans*-1(10)-*cis*-4-germacrene isoacoragermacrone (**6a**).[13] The ^1H NMR suggested the presence of a *trans*-1(10)-*cis*-4-germacrene in that the C-10 methyl group is deshielded relative to the expected chemical shift in a *trans*-1(10)-*trans*-4 isomer.[13] The structures of the three elemanes were assigned by a detailed study of their proton and carbon-13 NMR spectra[1b,14] (Table I) and a knowledge of their chemistry. Elemanes **8b** and **9b** were assigned the cis stereochemistry at the C-5 and C-10 divinyl groups since heating of either **8b** or **9b** in refluxing $CHCl_3$ for 24 h gave almost complete conversion to the *trans*-1(10)-*cis*-4-germacrene **6b**. A substantial amount of **8b** was also converted to **6b** upon attempted purification by $AgNO_3$/silica gel chromatography, and, therefore, **6b** had to be separated from **8b** by repeated recrystallizations. Fortunately **9b** could be separated from **6b** and **8b** by normal silica gel chromatography.

Both the ^1H and ^{13}C NMR supported the *cis*-divinyl stereochemistry assigned to **8b** and **9b**. The chemical shift for C-9 in **9b** was at a higher field than that in **8b** (δ 36.6 vs. 41.2), implying that either the C-5 or C-7 substituent in **9b** was axial whereas both of these substituents were equatorial in the most stable conformation of **8b**.[14] The lower field chemical shift of C-6 in **9b** relative to that in **8b** confirmed the trans relationship of the C-5 and C-7 substituents since a 3-ppm downfield shift is observed when the C-5 and C-7 substituents in the epimers of shyobunone are trans.[14b] The proton NMR spectra of **8b** and **9b** were almost identical except for H-5 and the protons of the isopropyl group. This confirmed that the divinyl groups of **8b** and **9b** were probably both diequatorial, and the only difference was in the relative orientation of the isopropyl groups.

The minor product **10b** was assigned the structure shown on the basis of the ^1H and ^{13}C NMR spectra. Proton NMR showed a large difference in chemical shifts for all the vinyl protons and the C-10 methyl group, indicating a trans orientation of the vinyl groups. The chemical shift of C-6 was in agreement with a trans arrangement of the C-5 and C-7 substituents.[14b] This was supported by the upfield shift in C-9 caused by the axial orientation of one of these substituents.[14b]

Thermolysis of **3b** in a sealed tube at 210 °C in benzene for 3 h gave the *trans*-decalin ester **7b** as the only isolated product in 90% yield. If, however, the thermolysis is carried out at a lower temperature and for a shorter period of time (195 °C, 20 min), the *trans*-1(10)-*cis*-4-cyclodecadiene **6b** can be isolated in low yield.[6c] Thermolysis of **6b** afforded **7b**, which supports the proposed mechanism that **6b** was the intermediate for the conversion of **3b** to **7b**. The isomerization of **6b** to **7b** involved an intramolecular ene reaction. This transannular reaction has been proven in the case where R = CH_3[1b] and was known to occur readily in similar germacrane systems.[13,15] The structure of **7b** was suggested by ^1H NMR which showed both an α,β-unsaturated ester (H-5, δ 7.25) as well as an exocyclic methylene group (H-14, δ 4.92, 4.66). Furthermore, the ^{13}C NMR spectral data of **7b** and related cadinanes is given in Table II. This data confirms the presence of the *trans*-decalin ring system and that the relative stereochemistry of the C-6 hydroxyl group and the C-7 isopropyl group was cis. Ultimately, this structure was confirmed by conversion of **7b** to (+)-isocalamendiol (**14b**) which is enantiomeric to the naturally occurring product.[8]

The synthesis of (+)-isocalamendiol (**14b**) from **7b** required the stereospecific oxygenation of the C-10(14) olefin and conversion of the α,β-unsaturated ester to an exocyclic methylene. The second part of this synthesis proved to be a problem. If the C-6 tertiary alcohol was not protected in the sequence, catalytic reduction of the C-4(5) olefin gave an α-ester, **12a**, which upon hydride reduction afforded an α-hydroxymethyl compound, **12b**. Any attempt to eliminate this alcohol resulted in the formation of an ether, **13a**. All attempts at epimerization of the α-ester **12a** to the more thermodynamically stable equatorial β isomer resulted in either recovery of starting material or formation of the lactone **13b**.

This problem was overcome by the initial protection of the C-6 alcohol as its β-[(methoxyethoxy)methyl] (MEM) ether, **11b**.[16] This was accomplished by refluxing a solution of **7b** in CH_3CN with $MEM^+NEt_3^-Cl$ for 18 h to give an 80% yield of the ether **11b**. Stereospecific hydration of **11b** using 1 equiv of $Hg(OAc)_2$ followed by basic reduction gave the diol **11c**.[17] Catalytic reduction of **11c** followed by reduction with $LiAlH_4$ gave the protected triol **12c**. The C-15 primary alcohol was converted selectively to an exocyclic methylene (**14a**) by utilizing the modified procedure of Grieco et al.[18a] It was found that use of

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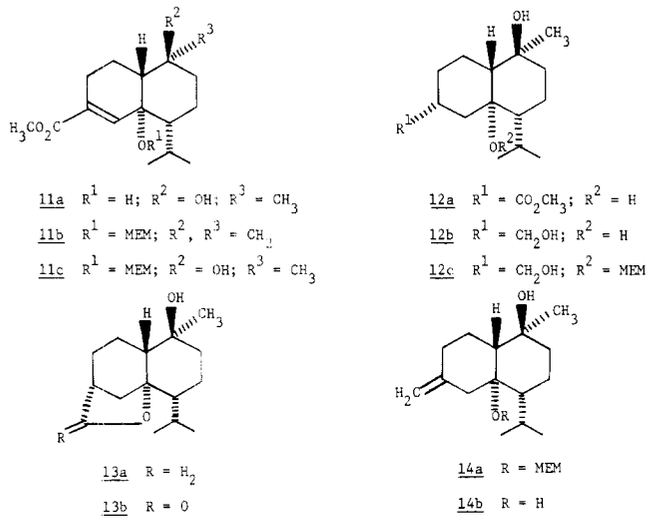

11a R^1 = H; R^2 = OH; R^3 = CH_3

11b R^1 = MEM; R^2, R^3 = CH_2

11c R^1 = MEM; R^2 = OH; R^3 = CH_3

12a R^1 = CO_2CH_3; R^2 = H

12b R^1 = CH_2OH; R^2 = H

12c R^1 = CH_2OH; R^2 = MEM

13a R = H_2

13b R = O

14a R = MEM

14b R = H

$NaIO_4$ as the oxidant gave a much better yield of the olefin **14a**.[18b] The MEM protecting group was then removed by using $ZnBr_2$[16] to give (+)-isocalamendiol (**14b**) whose spectral data were identical with those of natural material except for the sign of the rotation.[8]

In conclusion it can be seen that this photolysis–thermolysis reaction sequence can lead to a variety of germacrane, elemane, and cadinane sesquiterpenes in optically active form. Also the series of thermolysis experiments suggest that the *trans*-1(10)-*cis*-4-germacrene **6b** was the stable intermediate between the photoadduct **3b** and the *trans*-decalin **7b**. However, the results of the flash thermolysis suggested that the elemanes **8b** and **9b** may come directly from the photoadduct **3b** since they were readily converted to **6b** in refluxing chloroform.

This sequence also demonstrates the remarkable versatility of the MEM group for the protection of hydroxyl groups. It was possible to generate an MEM ether of a highly hindered tertiary alcohol and then remove it without affecting a second tertiary alcohol or the exocyclic methylene.

It is interesting to note that if dehydration of the primary alcohol in **12c** is attempted by using *p*-toluenesulfonyl chloride followed by diazabicycloundecane (DBU) the MEM group was lost and an ether, **13a**, resulted.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. IR spectra were taken with a Perkin-Elmer 137 Infracord spectrophotometer. ^{13}C NMR spectra were recorded at 25.16 MHz on a Varian XL-100 spectrometer fitted with a Nicolet 1180 pulse system, and ^1H NMR spectra were recorded at 90 MHz on a Perkin-Elmer R32 spectrometer. Chemical shifts are reported in δ units from the internal standard Me_4Si in chloroform-*d*. Optical rotations were measured at the sodium D line on a Perkin-Elmer 241 polarimeter using a 1-dm cell with methanol as the solvent. Circular dichroism spectra were measured on a JASCO J-41A spectropolarimeter using methanol as the solvent. High-resolution mass spectra were taken by using a Hitachi Perkin-Elmer RMH-2. TLC was carried out on silica gel GF plates, and column chromatography was performed by using Woelm silica gel.

2-(Carbomethoxy)-6-methyl-9-(1-methylethyl)tricyclo[4.4.0.0^{2,5}]decan-10-one (3b). Methyl cyclobutenecarboxylate (**1b**) was prepared according to literature methods[4] from commercially available cyclobutanecarboxylic acid. (–)-Piperitone (**2**) was synthesized from (+)-*trans*-piperitol which was supplied by Glidden Organics.

A typical photolysis follows. (–)-Piperitone [**2**; 4.38 g (28.8 mmol), $[\alpha]_D$ –30.5° (*c* 0.334 g/mL), 61% ee] and methyl cyclobutenecarboxylate (**1b**; 3.23 g, 28.8 mmol) were added to CH_2Cl_2 (4.0 mL) in a quartz test tube. This tube was sealed with a septum under Ar and the mixture photolyzed at –78 °C (dry ice–2-propanol) by using a 450-W Hanovia medium-pressure mercury lamp in a quartz well until the vinyl proton of the ester (**1b**) disappeared in the NMR. Then about 3.50 g (31.2 mmol) of **1b** was added, and the solution was photolyzed until the olefinic proton from **2** disappeared in the NMR. The solvent was removed, and the crude product was separated by silica gel chromatography (4% ether–petroleum ether) to give 5.684 g (74.7%) of pure product **3b**. Recrystallization from hexane gave about 40% recovery of optically pure product: mp 57–58 °C; IR (KBr) 1736, 1692 cm^{-1}; NMR 3.62 (s, 3 H), 2.90 (s, 1 H), 1.22 (s, 3 H), 0.93 (d, 3 H, J = 7.6 Hz), 0.81 (d, 3 H, J = 7.6 Hz); CD (methanol) $[\Theta]_{352}$ 0, $[\Theta]_{310}$ +9250, $[\Theta]_{256.5}$ +198, $[\Theta]_{237}$ +1660, $[\Theta]_{226}$ 0.

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.94; H, 9.06.

10-Hydroxy-6-methyl-9-(1-methylethyl)tricyclo[4.4.0.0^{2,5}]decane-2-carboxylic Acid γ-Lactone (4). The photoadduct **3b** (0.300 g, 1.13 mmol) was added to methanol containing a trace of methyl orange indicator. Then $NaBH_3CN$ (0.142 g, 2.25 mmol) was added, and the solution was stirred and kept at pH $\simeq$3 (pink color) by addition of methanolic HCl (saturated solution). The reaction was stirred at room temperature for 1 h after no color change was observed. The methanol was removed under reduced pressure and the crude product separated by extraction with water and ether. The ether extracts were combined, dried (anhydrous $MgSO_4$) and evaporated. Flash chromatography (10% ethyl acetate–hexane) yielded 0.122 g (46%) of **4**: mp 78.5–79 °C; IR (KBr) 1741 cm^{-1}; NMR δ 4.68 (d, 1 H, J = 9.6 Hz), 2.55 (d, 1 H, J = 9.6 Hz), 1.25 (s, 3 H), 0.90–1.10 (m, 6 H).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.87; H, 9.68.

Thermolysis of 10-Hydroxy-6-methyl-9-(1-methylethyl)tricyclo[4.4.0.0^{2,5}]decan-2-carboxylic Acid γ-Lactone (4). The lactone **4** (0.166 g, 0.708 mmol) was added to dry benzene (1.0 mL) and sealed in a tube under argon. The tube was heated at 210 °C for 6 h to give 0.097 g (58.4%) of the germacrane **5** after silica gel chromatography (5% ether–hexane): mp 93–94 °C; IR (KBr) 3054, 2903, 1744, 1643 cm^{-1}; NMR δ 7.25 (br s, 1 H), 4.92–5.45 (m, 2 H), 1.59 (s, 3 H), 1.11 (d, 3 H, J = 6 Hz), 1.04 (d, 3 H, J = 6 Hz); ^{13}C NMR δ 173.9 (s), 147.4 (d), 138.6 (s), 133.5 (s), 119.9 (d), 81.2 (d), 48.0 (d), 28.4 (t), 27.1 (d), 26.6 (t), 23.9 (t), 22.7 (q), 22.4 (t), 21.6 (q), 20.5 (q).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.70, H, 9.34.

Thermolysis of 2-(Carbomethoxy)-6-methyl-9-(1-methylethyl)tricyclo[4.4.0.0^{2,5}]decan-10-one (3b). (a) Sealed Tube Method. The photoadduct **3b** (0.125 g, 0.473 mmol) was added to dry benzene (0.7 mL) and sealed in a tube under argon. The tube was then heated at 210 °C for 6 h to give **7b** in quantitative yield: IR (neat) 3509, 1718, 1650 cm^{-1}; NMR δ 7.25 (s, 1 H), 4.92 (s, 1 H), 4.66 (s, 1 H), 3.74 (s, 3 H), 0.97 (d, 6 H, J = 8 Hz).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.90; H, 9.13.

(b) Refluxing Solvent Method. The photoadduct **3b** (0.551 g, 2.08 mmol) was added to *n*-decane (8 mL) and refluxed for 15 h. Flash chromatography of the crude product mixture (10% ethyl acetate–hexane) gave 0.432 g (78.4%) of **7b**.

(c) Vacuum Pyrolysis Method. The photoadduct **3b** (1.918 g, 7.26 mmol) in petroleum ether (4 mL) was passed over hot quartz chips at 500 °C under vacuum. Purification by silica gel chromatography yielded 0.264 g (18.7%) of the germacrene **6b** and 0.38 g (27%) of the mixture of elemanes **8b**, **9b**, and **10b** in a relative ratio of 49:43:8 as well as 0.189 g (13.4%) of **7b**. The germacrane **6b** and elemanes **8b**, **9b**, and **10b** were separated by chromatography using 15% $AgNO_3$ impregnated silica gel (benzene–hexane). Germacrene **6b**: mp 89–90 °C; IR (KBr) 1726, 1688, 1631 cm^{-1}; ^1H NMR δ 7.20 (s, 1 H), 5.25–4.86 (m, 1 H), 3.78 (s, 3 H), 1.47 (s, 3 H), 1.01 (d, 3 H, J = 8.0 Hz), 0.96 (d, 3 H, J = 8.0 Hz); ^{13}C NMR δ 204.8 (s), 167.6 (s), 140.3 (d), 139.2 (s), 135.0 (s), 123.9 (d), 58.0 (d), 52.1 (q), 40.4 (t), 31.0 (d), 26.6 (t), 25.2 (t), 23.6 (t), 20.7 (q), 19.6 (q), 14.5 (q); $[\alpha]_D$ +28.5 (*c* 0.0248 g/mL).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.87; H, 9.38.

Elemane **8b**: IR (neat) 1720, 1627 cm^{-1}; NMR δ 6.55 (s, 1 H), 5.84 (s, 1 H), 5.86 (dd, 1 H, J = 12, 18 Hz), 5.10 (d, 1 H, J = 12

Table II. Carbon-13 NMR Spectral Data of Cadinane Compounds[a]

carbon	compd								
	7b	11b	11c	12a	12c	13a	13b	14a	14b
1	48.6	48.6	50.1	54.9	56.3	54.3	51.1	55.9	54.1
2	19.6	19.3	15.6	17.3	16.7	19.7	19.6	21.3	22.9
3	24.8	24.9	25.3	27.5	26.3	30.0	26.2	34.4	34.7
4	132.5	135.7	135.1	38.1	34.4	35.2	39.9	145.6	146.0
5	138.5	136.1	136.0	36.9	30.3	41.6	40.3	41.4	46.9
6	71.7	78.2	77.1	73.1	79.7	85.5	88.6	80.2	74.9
7	49.8	51.6	52.2	52.2	54.6	46.7	47.2	53.5	51.4
8	22.4	22.9	19.7	18.9	21.4	20.2	19.7	20.3	19.4
9	35.6	35.7	41.9	42.8	43.4	42.7	42.0	42.9	43.1
10	148.5	148.8	71.7	72.3	72.2	72.5	71.5	72.3	72.5
11	25.8	25.5	24.4	25.0	24.2	25.3	25.1	24.5	25.3
12	23.3	24.2	24.2	23.0	23.5	23.2	23.0	23.1	23.1
13	17.9	18.0	17.9	18.2	18.6	18.5	18.3	18.3	18.4
14	108.0	106.1	22.0	23.9	27.0	23.8	23.7	25.2	24.0
15	167.6	167.2	166.9	178.2	64.6	73.3	178.4	110.0	111.4
OMe	51.4	51.6	51.2	51.9					
16		91.3	91.7		90.4			90.8	
17		71.6	71.2		71.4			71.5	
18		67.0	66.9		67.3			67.3	
19		58.7	58.3		58.6			58.6	

[a] The MEM group is numbered $O^{16}H_2OC^{17}H_2C^{18}H_2OC^{19}H_3$.

Hz), 4.98 (d, 1 H, J = 18 Hz), 3.39 (s, 1 H), 3.70 (s, 3 H), 1.12 (s, 3 H), 0.93 (d, 3 H, J = 8 Hz), 0.89 (d, 3H, J = 8 Hz); CD $[\theta]_{293}$ −1114.

Elemane **9b**: mp 44–50 °C; IR (KBr) 1708, 1633 cm^{-1}; NMR δ 6.56 (s, 1 H), 5.86 (s, 1 H), 5.98 (dd, 1 H, J = 10, 17 Hz), 5.10 (d, 1 H, J = 10 Hz), 4.99 (d, 1 H, J = 17 Hz), 4.06 (s, 1 H), 3.72 (s, 3 H), 1.12 (s, 3 H), 1.02 (d, 3 H, J = 7 Hz), 0.88 (d, 3 H, J = 7 Hz); CD $[\theta]_{295}$ +9696; mass spectrum, calcd for $C_{16}H_{24}O_3$ m/e 264.1725, found m/e 264.1735.

Elemane **10b**: IR (neat) 1714, 1621 cm^{-1}; NMR δ 6.16 (s, 1 H), 5.61 (s, 1 H), 5.52–5.96 (m, 1 H), 4.86–5.22 (m, 2 H), 3.70 (s, 4 H), 1.22 (s, 3 H), 0.92 (d, 3 H, J = 8 Hz), 0.89 (d, 3 H, J = 8 Hz); mass spectrum, calcd for $C_{16}H_{24}O_3$ m/e 264.1725, found m/e 264.1725.

1-Methyl-4-(1-methylethyl)-6-(carbomethoxy)-1,2,3,4,7,8-hexahydro-1,4a-naphthalenediol (11a). Mercuric acetate (1.707 g, 5.36 mmol) was added to H_2O (15 mL) and THF (15 mL) followed by 1.287 g (4.87 mmol) of **7b**, and the reaction was stirred for 1 h at room temperature. Then 3 M NaOH (9.0 mL, aqueous) and 0.5 M $NaBH_4$ in 3 M NaOH (5.4 mL, aqueous) were added and the mixture was stirred for 15 min. The mercury was allowed to settle out, and the reaction mixture was decanted and then extracted with water and ether. The combined ether extracts were dried and evaporated. The crude product was purified by column chromatography (10% ethyl acetate–petroleum ether) to give 1.005 g (73%) of **11a**: mp 136–138 °C; IR (KBr) 3432, 3329, 1705, 1641 cm^{-1}; NMR δ 7.20 (s, 1 H), 3.77 (s, 3 H), 1.27 (s, 3 H), 1.00 (d, 6 H, J = 8 Hz).

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 67.96; H, 8.90.

1-Methyl-4-(1-methylethyl)-6-(carbomethoxy)octahydro-1,4a-naphthalenediol (12a). The diol **11a** (0.228 g, 0.80 mmol) was added to ethyl acetate (18 mL) and PtO_2 (0.030 g), and the solution was treated with H_2 at room temperature and 1 atm pressure for 24 h. The solvent was removed and the crude product purified by flash chromatography (20% ethyl acetate–hexane) to give 0.115 g (50%) of **12a**: IR (KBr) 3432, 1705 cm^{-1}; NMR δ 3.77 (s, 3 H), 1.25 (s, 3 H), 0.95 (d, 6 H, J = 8 Hz).

Anal. Calcd for $C_{15}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.40; H, 9.57.

1-Methyl-4-(1-methylethyl)-6-(hydroxymethyl)octahydro-1,4a-naphthalenediol (12b). To a solution of $LiAlH_4$ (0.077 g, 2.02 mmol) in anhydrous ether (5 mL) was added **12a** (0.115 g, 0.404 mmol). The solution was then gently refluxed for 2 h. After the excess $LiAlH_4$ was quenched (cold H_2O), the solution was filtered, dried, and evaporated. Purification by flash chromatography (30% ethyl acetate–hexane) yielded 0.086 g (83%) of **12b**: IR (neat) 3333 cm^{-1}; NMR δ 3.78 (d, 2 H, J = 6 Hz), 1.23 (s, 3 H), 0.95 (d, 3 H, J = 8 Hz), 0.90 (d, 3 H, J = 8 Hz).

Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.26; H, 11.06.

Cyclization of 1-Methyl-4-(1-methylethyl)-6-(hydroxymethyl)octahydro-1,4a-naphthalenediol (12b). A solution of **12b** (0.032 g, 0.125 mmol) in pyridine (0.6 mL) was treated with methanesulfonyl chloride (0.019 mL, 0.250 mmol) at 5 °C for 23 h. The mixture was poured onto ice and extracted with ether, and the combined ether extracts were dried and evaporated. The crude mesylate was added to dry benzene (5 mL) and DBU (0.037 mL, 0.250 mmol) and stirred for 2 h. Purification of the crude product by silica gel chromatography (10% ether–hexane) gave 0.016 g (54%) of **13a**: mp 115–115.5 °C; IR (KBr) 3329 cm^{-1}; NMR δ 3.80 (d, 2 H, J = 2.4 Hz), 1.22 (s, 3 H), 0.92 (d, 3 H, J = 8 Hz), 0.87 (d, 3 H, J = 8 Hz).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.31; H, 11.34.

Lactonization of 1-Methyl-4-(1-methylethyl)-6-(carbomethoxy)octahydro-1,4a-naphthalenediol (12a). The ester **12a** (0.35 g, 1.26 mmol) was added to a solution of sodium (1.0 g, 43.0 mmol) in dry methanol (13 mL), and this solution was refluxed for 6 h and then stirred for 10 h at room temperature. The solution was then neutralized and evaporated. The crude product was extracted with ether–5% HCl(aq), and the combined ether extracts were dried and evaporated. Any free acids were converted to their respective methyl esters by using excess ethereal diazomethane. Flash silica gel chromatography (20–50% ethyl acetate–petroleum ether) gave 0.133 g (42%) of lactone **13b** as well as recovered starting material **12a**. For compound **13b**: mp 109–115 °C; IR (KBr) 3517, 1757 cm^{-1}; NMR δ 1.23 (s, 3 H), 0.97 (d, 3 H, J = 6 Hz), 0.90 (d, 3 H, J = 6 Hz).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.26; H, 9.64.

1-Methylene-4-(1-methylethyl)-4a-[(methoxyethoxy)methyl]-6-(carbomethoxy)-1,2,3,4,7,8-hexahydronaphthalene (11b). The alcohol **7b** (0.859 g, 3.25 mmol) was added to dry acetonitrile (25 mL) with $MEM^+NEt_3^-Cl$ (9.06 g, 40.2 mmol) and the reaction stirred at reflux for 63 h. The crude product was extracted with water–ether, and the combined organic layers were dried and evaporated. The crude product was purified by flash chromatography (7% ethyl acetate–hexane) to give 0.798 g of **11b** as well as 0.109 g of **7b**. The corrected yield was 80%. Compound **11b**: IR (neat) 1724, 1653 cm^{-1}; NMR δ 7.17 (br s, 1 H), 4.94–4.57 (m, 4 H), 3.81 (s, 3 H), 3.77–3.45 (m, 4 H), 3.37 (s, 3 H), 0.98 (d, 3 H, J = 8 Hz), 0.93 (d, 3 H, J = 8 Hz).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.49; H, 9.37.

1-Methyl-4-(1-methylethyl)-4a-[(methoxyethoxy)methyl]-6-(carbomethoxy)-1,2,3,4,7,8-hexahydro-1-naphthalenol (11c). Mercuric acetate (3.47 g, 10.9 mmol) was added to THF (32 mL) and water (32 mL) followed by **11b** (3.485 g, 9.89 mmol), and the subsequent solution was stirred for 1 h at room temperature. Then 3 N NaOH (8.0 mL, aqueous) and

0.5 N $NaBH_4$ in 3 N NaOH (8.0 mL, aqueous) were added and the mixture stirred for 15 min. The mercury was allowed to settle, the solution was diluted with ether, and the combined ether extracts were dried and evaporated. The crude product was purified by column chromatography to give 2.585 g (71%) of **11c**: IR (neat) 3425, 1715, 1639 cm^{-1}; NMR δ 7.07 (br s, 1 H), 3.84-3.70 (m, 3 H), 3.76 (s, 3 H), 3.71-3.39 (m, 4 H), 3.34 (s, 3 H), 1.26 (s, 3 H), 0.99 (d, 3 H, J = 8 Hz), 0.93 (d, 3 H, J = 8 Hz).

Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.66; H, 9.29.

1-Methyl-4-(1-methylethyl)-4a-[(methoxyethoxy)-methyl]-6-(hydroxymethyl)octahydronaphthalenol (12c). The ester **11c** (0.248 g, 0.669 mmol) was added to ethyl acetate (18 mL) with PtO_2 (0.035 g) and treated with H_2 (room temperature and 1 atm) for 24 h. The Pt was filtered off, and the solvent was removed to give 0.236 g of crude product. This was added to a solution of $LiAlH_4$ (0.120 g, 3.17 mmol) in dry ether (5 mL), and the solution was refluxed for 2 h. After the mixture cooled, the product was extracted with ether and water, and the ether extracts were dried and evaporated. The crude product was purified by using flash chromatography (30% ethyl acetate-hexane) to give 0.196 g (85%) of **12c**: IR (neat) 3378 cm^{-1}; NMR δ 4.96-4.60 (m, 2 H), 3.96-3.38 (m, 6 H), 3.31 (s, 3 H), 1.16 (s, 3 H), 0.88 (d, 3 H, J = 10 Hz), 0.81 (d, 3 H, J = 10 Hz).

Anal. Calcd for $C_{19}H_{36}O_5$: C, 66.24; H, 10.53. Found: C, 66.40; H, 10.31.

1-Methyl-4-(1-methylethyl)-4a-[(methoxyethoxy)-methyl]-6-methyleneoctahydro-1-naphthalenol (14a). The alcohol **12c** (0.433 g, 1.26 mmol) was added to a solution of (*o*-nitrophenyl)selenyl cyanide (0.343 g, 1.51 mmol) in THF (4.5 mL) at room temperature under N_2. Tri-*n*-butylphosphine (0.376 mL, 1.51 mmol) was added dropwise, and the reaction was stirred for 2 h. The solvent was removed under reduced pressure and purified by using flash chromatography to give 0.520 g (78%) of selenide. This was added to a solution of $NaHCO_3$ (0.95 g, 1.10 mmol) and $NaIO_4$ (0.488 g, 2.28 mmol) in methanol (17 mL) and water (3.0 mL). The solution was stirred for 90 min and then extracted with ether and $NaHCO_3$(aq). The combined ether layers were dried and evaporated. Flash chromatography (10% ethyl acetate-petroleum ether) yielded 0.229 g (56%) of **14a**: IR (neat) 3448, 3058, 1646 cm^{-1}; NMR δ 5.10-4.87 (m, 2 H), 4.76 (br s, 2 H), 3.94-3.43 (m, 4 H), 3.37 (s, 3 H), 1.24 (s, 3 H), 0.97 (d, 3 H, J = 7 Hz), 0.90 (d, 3 H, J = 7 Hz).

Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 70.04; H, 10.53.

(+)-Isocalamendiol (14b). The protected diol **14a** (0.085 g, 0.260 mmol) was added to dry CH_2Cl_2 (8.6 mL) at 0 °C. Then $ZnBr_2$ (0.290 g, 1.3 mmol) was added, and the reaction was stirred at 0 °C for 24 h with small additions of $ZnBr_2$ every few hours. Then concentrated aqueous NH_4OH was added, and the resulting mixture was diluted with water and extracted with ether. The combined ether extracts were dried and evaporated. Chromatography on silica gel (10% ethyl acetate-pentane) yielded 0.021 g (44%) of (+)-isocalamendiol (**14b**) as well as 0.019 g of starting material **14a**: IR (neat) 3390, 3049, 1650 cm^{-1}; NMR δ 4.87 (s, 1 H), 4.75 (s, 1 H), 1.22 (s, 3 H), 0.97 (d, 3 H, J = 8 Hz), 0.94 (d, 3 H, J = 8 Hz); $[\alpha]_D$ +17.6° (*c* 0.0128 g/mL).

Synthetic (+)-isocalamendiol (**14b**) was identical in all respects, IR and ^1H and ^{13}C NMR, with authentic (-)-isocalamendiol except in the sign of rotation, $[\alpha]_D$ -26.6° (*c* 0.0092 g/mL).

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Cyanoketenes. Mechanism of *tert*-Butylcyanoketene Cycloaddition to Aldo- and Ketoketenes

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tert-Butylcyanoketene cycloadds to ketene, methylketene, dimethylketene, and ethylmethylketene. The first two examples give 2-oxetanones and the last two result in cyclobutane-1,3-diones. These cycloadditions are shown to proceed by a nonconcerted dipolar mechanism involving zwitterionic intermediates. Establishment of the intermediacy of the zwitterions was accomplished by their independent generation from the thermolysis of substituted 4-azido-5-*tert*-butylcyclopentene-1,3-dione precursors. The mechanistic consequences of these cycloadditions and how they may apply to other ketene dimerizations are discussed.

Introduction

Reported here is an investigation of the cycloaddition of *tert*-butylcyanoketene (TBCK) to a series of aldo- and ketoketenes.[1] It will be shown that such [2 + 2] cycloadditions proceed by a stepwise process involving zwitterionic intermediates and that these ring close to cyclobutane-1,3-diones or 2-oxetanones when generated from TBCK and, respectively, keto- or aldoketenes. This study was stimulated primarily by the fact that ketene dimerizations, in general, are fraught with ambiguities regarding the operative mechanism. Indeed, no clear unambiguous data has appeared which firmly establishes the concerted or nonconcerted nature of a ketene dimerization. Dehmlow, Stopianka and Pickardt[2] have recently shown that dimerizations of alkylphenyl- and alkylbenzylketenes give increasing amounts of *Z*-enriched cyclobutane-1,3-diones as the steric bulk of the ketene increases. In one case, isopropylphenylketene, only the *Z* isomer was observed. This enhancement of the *Z* stereoisomer is in agreement with the predictions arising from a concerted $[_\pi 2_s + _\pi 2_a]$ mechanism. However, the total yields of the cycloadducts are very low (3-56%) and thus mechanistic interpretations

(1) A preliminary account of this work has appeared. See H. W. Moore and D. Scott Wilbur, *J. Am. Chem. Soc.*, **100**, 6523 (1978).

(2) E. V. Dehmlow, M. Stopianka, and J. Pickardt, *Liebigs Ann. Chem.*, 572 (1979).

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