Synthesis and Pheromone Activities of Optically Active Neocembrenes and Their Geometrical Isomers, (*E,Z,E*)- and (*E,E,Z*)-Neocembrenes[1]

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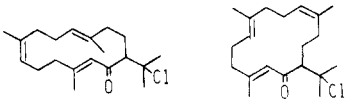
In order to investigate the scope of the intramolecular acylation reaction of geranylgeranioic acid chloride (Ia), which has been demonstrated to give the chloro ketone IIa in high yield, the isomeric acid chlorides Ib and Ic were subjected to the action of $SnCl_4$. The increased reactivity of the terminal double bond in each compound was observed, leading to the exclusive formation of the corresponding chloro ketones IIb and IIc, which were converted into the geometrically isomeric neocembrenes Vb and Vc, respectively. *d*- and *l*-neocembrenes were prepared from the corresponding trans menthoxyacetyl esters XXI and XXII. The trail-laying bioassay revealed that stereoisomerism rather than optical isomerism is the most important factor for pheromone activity.

A termite trail pheromone, neocembrene (Va), was characterized by one of us (B.P.M.) as a diterpene hydrocarbon possessing a 14-membered cembrene skeleton.[2] In conjunction with general cembrenoid chemistry, we have engaged in a detailed exploration of a construction method for this macrocyclic ring system[3] and have described an efficient synthesis of *dl*-neocembrene.[4] At the same time, we have shown that the *dl* form shows the same order of activity as that of the natural pheromone.

As shown in Scheme I, the synthesis was carried out starting from the chloro ketone IIa, which was prepared by $SnCl_4$-induced cyclization of (*E,E,E*)-geranylgeranioic acid chloride (Ia). Notwithstanding the presence of four double bonds in the molecule, the intramolecular acylation occurs regioselectively at the terminal double bond, leading to the formation of the chloro ketone in 70% yield. In terms of simplicity and efficiency, this method presents an unparalleled opportunity for the construction of the cembrene skeleton.[5]

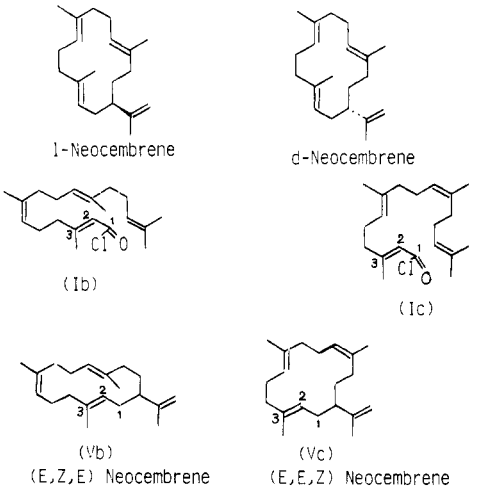
In order to investigate the scope of this acylation reaction, it seemed worthwhile to examine the cyclization of geometrical isomers of Ia. When the isomeric (*E,Z,E*)- and (*E,E,Z*)-geranylgeranioic acid chlorides (Ib and Ic) are subjected to the action of $SnCl_4$ under the same conditions, the resulting products would have 10- or 14-membered rings, depending on the acylation position of the double bond of the molecule. If increased reactivity of the terminal double bond could be observed, it might be exploited in the synthesis of geometrically isomeric (*E,Z,E*)- and (*E,E,Z*)-neocembrenes (Vb and Vc) from the corresponding chloro ketones IIb and IIc.

As a contribution to our understanding of pheromone activity in relation to chemical structure, it would be of particular interest to examine the activities of these isomeric neocembrenes. Furthermore, it would be desirable to prepare *d*- and *l*-(*E,E,E*)-neocembrenes and to submit each enantiomer to the trail-laying bioassay. In this way, it could be possible to determine the absolute configuration of the naturally occurring neocembrene.



(IIb) (IIc)

This paper is concerned with the synthesis of geometrically isomeric neocembrenes (Vb and Vc) and also the optically active neocembrenes, as well as the examination of the pheromone activities of these compounds.



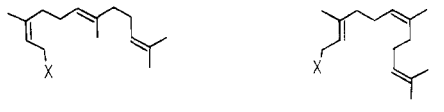
l-Neocembrene d-Neocembrene

(Ib) (Ic)

(Vb) (Vc)

(E,Z,E) Neocembrene (E,E,Z) Neocembrene

Preparation of (*E,Z,E*)- and (*E,E,Z*)-Neocembrenes. The starting materials for (*E,Z,E*)- and (*E,E,Z*)-geranylgeranioic acid chlorides (Ib and Ic) were derived from the corresponding (*Z,E*)- and (*E,Z*)-farnesols (VIb and VIc), respectively.[6] Farnesylacetones (IXb and IXc)



(VIb) X = OH
(VIIb) X = Br
(VIIIb) X = $CH(CO_2Et)COMe$
(IXb) X = CH_2COMe
(Xb) X = $CH_2C(Me)=CHCO_2Et$

(VIc) X = OH
(VIIc) X = Br
(VIIIc) X = $CH(CO_2Et)COMe$
(IXc) X = CH_2COMe
(Xc) X = $CH_2C(Me)=CHCO_2Et$

(1) This constitutes part 33 of this series by Kato's group: Part 32: T. Kato and I. Ichinose, *J. Chem. Soc., Perkin Trans. 1*, in press. Part 31: I. Ichinose and T. Kato, *Chem. Lett.*, 61 (1979).

(2) (a) B. P. Moore, *Nature (London)*, 211, 746 (1966); (b) A. J. Birch, W. V. Brown, J. E. T. Corrie, and B. P. Moore, *J. Chem. Soc., Perkin Trans. 1*, 2653 (1972).

(3) T. Kato, T. Kobayashi, and Y. Kitahara, *Tetrahedron Lett.*, 3299 (1975).

(4) Y. Kitahara, T. Kato, T. Kobayashi, and B. P. Moore, *Chem. Lett.*, 219 (1976).

(5) Other syntheses of the cembrene skeleton: (a) W. G. Dauben, G. H. Beasley, M. D. Broardhurst, B. Muller, D. J. Peppard, P. Pesnelle, and C. Suter, *J. Am. Chem. Soc.*, 97, 4973 (1975); (b) M. Kodama, Y. Matsuki, and S. Ito, *Tetrahedron Lett.*, 3065 (1975); (c) L. Crombie, G. Kneen, and G. Pattenden, *J. Chem. Soc., Chem. Commun.*, 66 (1976); (d) H. Takayanagi, T. Uyehara, and T. Kato, *ibid.*, 359 (1978).

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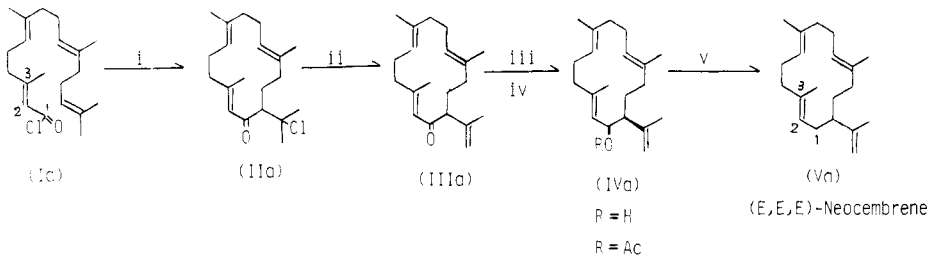
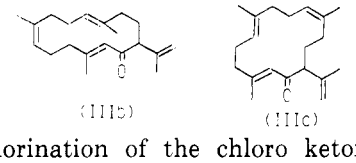
Scheme I

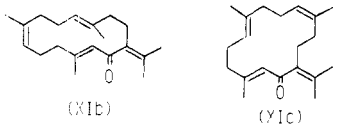


were prepared by alkylation of ethyl sodioacetoacetate with the corresponding farnesyl bromides (VIIb and VIIc) followed by hydrolysis and decarboxylation of the resulting β-keto esters VIIIb and VIIIc.[7] Condensation of farnesylacetones with the sodium salt of triethyl phosphonoacetate afforded (*E,Z,E*)- and (*E,E,Z*)-ethyl geranylgeranioates (Xb and Xc), which, after purification by silica gel chromatography to remove a small amount of 2,3-cis isomer, were hydrolyzed and finally converted into the acid chlorides Ib and Ic by the action of thionyl chloride.

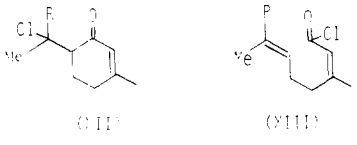
Each of the acid chlorides Ib and Ic was cooled to −78 °C and treated with 0.3 mol equiv of $SnCl_4$. Within 30 min, complete acylation had occurred. After the reaction was quenched with water, the chloro ketones IIb and IIc were obtained as the exclusive products. Careful analysis of the crude reaction mixture in each instance afforded no indication of the presence of any 10-membered products. The chloro ketones were unstable on silica gel and were partially transformed into the isopropenyl ketones IIIb and IIIc during column chromatography with silica gel.[5d] The


(IIIb) (IIIc)

dehydrochlorination of the chloro ketones was also achieved by treatment with $LiBr/Li_2CO_3$, leading to the formation of IIIb and IIIc, accompanied by a small amounts of isopropylidene ketones XIb and XIc.

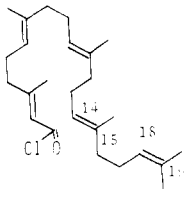

(XIb) (XIc)

Concerning the cyclization mode of geranylgeranioic acid chlorides, these and the previously described results[3] indicate that a 14-membered cembrene skeleton is constructed exclusively from any acid chloride having a 2,3-trans (*E*) double bond. The geometry of both C_6 and C_{10} double bonds in the molecule has no influence on the cyclization products. On the other hand, the six-membered-ring ketone XII was formed exclusively when the

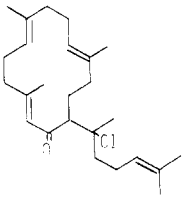

(XII) (XIII)

R = $(CH_2CH_2CH=C)_2$-Me
Me

2,3-cis (*Z*) isomer XIII was submitted to the cyclization under the same conditions.[8] It has also been demonstrated that geranylfarnesoic acid chloride (XIV), a C_{25} analogue

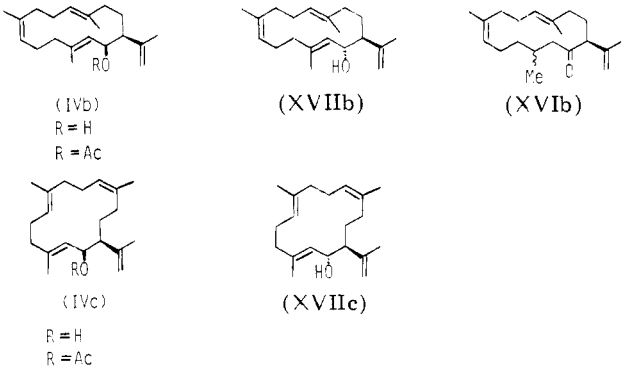

(XIV)

of I, gives exclusively the corresponding 14-membered-ring compound XV,[9] although inspection of a Dreiding model


(XV)

suggests that the C_{18}–C_{19} double bond of the molecule could interact with the acyl cation without any hindrance. Formation of a 14-membered ring might be thermodynamically more favored than that of an 18-membered ring. At present, the reason for this switch in mode of ring closure is not entirely clear.

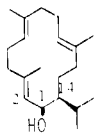
Reduction of isopropenyl ketones IIIb and IIIc with $LiAlH_4$ afforded, after purification with silica gel column chromatography, cis and trans alcohols IVb,c (R = H) and XVIIb,c accompanied by small amounts of 2,3-dihydro ketones XVIb. The stereochemistry of the resultant hy-


(IVb) (XVIIb) (XVIb)
R = H
R = Ac
(IVc) (XVIIc)
R = H
R = Ac

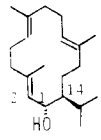
droxyl group with respect to the neighboring isopropenyl

(6) We are deeply grateful to Takasago Perfumery Co. Ltd. and Kurarey Co. Ltd. for their generous gift of the starting materials.
(7) E. E. van Tamelen and R. G. Nadeau, *J. Am. Chem. Soc.*, **89**, 176 (1967).
(8) T. Kobayashi, S. Kumazawa, T. Kato, and Y. Kitahara, *Chem. Lett.*, 301 (1975).
(9) T. Kato, M. Suzuki, Y. Nakazima, K. Shimizu, and Y. Kitahara, *Chem. Lett.*, 705 (1977).

moiety was deduced on the basis of ^1H NMR evidence. As described previously,[4] the C_1 protons of mukulol (XVIII) and of its epimer XIX appear as a doublet of doublets ($J_{1,2}$



(XVIII)

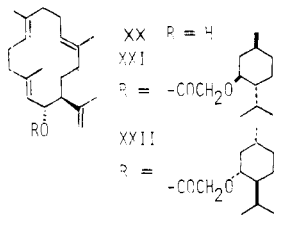


(XIX)

= 9, $J_{1,14}$ = 1 Hz) and as a triplet ($J_{1,2} = J_{1,14}$ = 9 Hz), respectively. In compounds IV (b and c) and XVII (b and c), the coupling modes of C_2–C_1–C_{14} are quite similar to those of XVIII and XIX,[10] indicating the assigned stereochemistry of IV and XVII, respectively.

The cis alcohols IVb and IVc (R = H), obtained as major products, were converted into the corresponding acetates IVb and IVc (R = Ac), which were reduced with Li in ethylamine to give geometrical isomers Vb and Vc of neocembrene (Va) in 43 and 35% overall yields, respectively.

Preparation of *d*- and *l*-Neocembrenes. Owing to the limited amounts of natural neocembrene available from termites, measurement of optical rotation has not yet been carried out. In the meantime, Dev and co-workers have independently isolated (−)-neocembrene from a plant[11] and determined the asymmetric carbon to have the *R* configuration. We have found that the menthoxyacetate of (*E*,*E*,*E*)-trans alcohol XX affords a route to the optical



resolution of *dl*-neocembrene. This ester demonstrates differential crystallization of the two enantiomers. The crystalline ester obtained from (*E*,*E*,*E*)-trans alcohol XX by the action of *l*-menthoxyacetyl chloride was repeatedly recrystallized from MeOH to give the ester XXI with $[\alpha]_D$ −89.0°. This ester was then reduced with Li in ethylamine to give (+)-neocembrene with $[\alpha]_D$ +19.5°. The enantiomer, (−)-neocembrene with $[\alpha]_D$ −19.0°, was prepared by a similar sequence of operations involving the *d*-menthoxyacetyl ester XXII. After repeated recrystallization from MeOH, pure ester XXII, $[\alpha]_D$ +88.0°, was obtained.

Pheromone Activities of Neocembrenes. The synthetic neocembrenes were tested for trail-laying activity in pure pentane (Nanograde) solutions, ranging in concentration from 10^{-4} to 10^{-8} g/mL. The tests were performed with workers and soldiers of the termite *Nasutitermes exitiosus* (Hill) at 25 °C, according to standard procedures.[12]

The resolved *d*- and *l*-(*E*,*E*,*E*)-neocembrenes showed activity of a high order and could not be differentiated from each other or from the racemic mixture in the biological test. The activity recorded was of the same order as that of the natural pheromone, although the latter was not available for direct comparison. Racemic (*E*,*Z*,*E*)-neocembrene showed weak activity, but only at concentrations some 10^3 times those required for the *E*,*E*,*E* isomer; racemic (*E*,*E*,*Z*)-neocembrene proved entirely inactive.

Thus although it has not proved possible to determine the absolute configuration of the natural pheromone by this means, the data do indicate that optical isomerism is not a significant factor in determining trail-laying activity. On the other hand, stereoisomerism affecting the conformation of the ring is evidently most important.

Experimental Section

Preparation of (*E*,*Z*,*E*)- and (*E*,*E*,*Z*)-Geranylgeranioic Acids. To a mixture of (*E*,*Z*)-farnesol (VIc) (4.27 g, 19.2 mmol) and triphenylphosphine (6.54 g, 25 mmol) in acetonitrile (40 mL) was added carbon tetrabromide (8.26 g, 25 mmol) and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the residue was extracted with *n*-hexane to obtain crude (*E*,*Z*)-farnesyl bromide (VIIc), which was used without purification for the next reaction. A mixture of the whole amount of the crude bromide VIIc, ethyl acetoacetate (7.49 g, 57.5 mmol), and anhydrous K_2CO_3 (3.98 g, 28.8 mmol) in dry acetone (40 mL) was refluxed for 3.5 h and the volatile materials were removed under reduced pressure. The resultant residue was taken into ether and the ether was removed after being washed with water and then dried over Na_2SO_4. The residue was passed through a SiO_2 column with *n*-hexane–AcOEt (20:1) to give (*E*,*Z*)-farnesyl keto ester VIIIc: 3.54 g, 55.2%; NMR (CCl_4) δ 1.27 (t, J = 7 Hz, 3 H) and 4.14 (q, J = 7 Hz, 2 H) (OEt), 1.67 (br s, 4 C=CMe), 2.14 (s, 3 H, COMe), 3.28 (t, J = 7 Hz, 1 H, MeCOC**H**FCO$_2$Et (F = farnesyl)), and 5.03 (br m, 3 C=CH).

A mixture of the farnesyl keto ester VIIIc (4.34 g, 13.0 mmol), MeOH (15 mL), and 5 N KOH (7.5 mL) was warmed at 80 °C for 2 h and, after cooling, acidified with 2 N aqueous HCl. The product mixture was extracted with ether, washed successively with water, aqueous $NaHCO_3$, and aqueous NaCl solutions, and dried over $MgSO_4$, and the solvent removed to give a residue which was passed through a SiO_2 column with *n*-hexane–AcOEt (20:1) to afford (*E*,*Z*)-farnesylacetone (IXc): 3.14 g, 92%; mass spectrum, m/e 262 ($C_{18}H_{30}O$ requires m/e 262.42); NMR δ 1.62 (s, 2 C=CMe), 1.67 (s, 2 C=CMe), 2.05 (s, COMe), and 5.06 (br m, 3 C=CH); IR (film) 1725 cm^{-1}.

Similarly, (*Z*,*E*)-farnesol (VIb) was converted into (*Z*,*E*)-farnesylacetone (IXb): mass spectrum, m/e 262 ($C_{18}H_{30}O$ requires m/e 262.42); NMR δ 1.61 (2 C=CMe), 1.67 (2 C=CMe), 2.04 (COMe), and 5.06 (br m, 3 C=CH).

A 55% oil dispersion of NaH (660 mg, 15 mmol) was washed three times with anhydrous benzene and then 20 mL of benzene was added. To this stirred suspension was gradually added triethyl phosphonoacetate (3.71 g, 16.5 mmol) and the stirring was continued until suspended NaH completely disappeared. (*E*,*Z*)-Farnesylacetone (IXc) (3.04 g) was added dropwise to this solution and the mixture was kept at room temperature for 40 h. After being washed with water and dried over $MgSO_4$, the solvent was removed and the residue was passed through a SiO_2 column with *n*-hexane–AcOEt (40:1) to give ethyl (*E*,*E*,*Z*)-geranylgeranioate (Xc) (3.0 g, 78%) and the isomeric ethyl (*Z*,*E*,*Z*)-geranylgeranioate (0.66 g, 17%), respectively. (*E*,*E*,*Z*)-Ester Xc: mass spectrum, m/e 332 ($C_{22}H_{36}O_2$ requires m/e 332.51); NMR δ 1.25 and 4.09 (OEt), 1.62 (s, 2 C=CMe), 1.68 (s, 2 C=CMe), 2.14 (d, J = 1.4 Hz, C_3-Me), 5.09 (br m, 3 C=CH), and 5.59 (br s, C_2-H). (*Z*,*E*,*Z*)-Ethyl geranylgeranioate: mass spectrum, m/e 332 ($C_{22}H_{36}O_2$ requires m/e 332.51); NMR δ 1.25 and 4.09 (OEt), 1.63 (2 C=CMe), 1.68 (2 C=CMe), 1.88 (d, J = 1.6 Hz, C_3-Me), 5.12 (br m, 3 C=CH), and 5.59 (br s, C_2-H).

A mixture of ethyl (*E*,*E*,*Z*)-geranylgeranioate (Xc) (2.14 g, 6.44 mmol) and 2 N KOH (16 mL) in dioxane (32 mL) was warmed at 85 °C for 10 h, then cooled, acidified with 2 N aqueous HCl, and extracted with ether. The ether solution was washed with water, dried over Na_2SO_4, and evaporated to give a crude acid which was chromatographed on a short SiO_2 column in *n*-hexane–AcOEt (10:1) to give pure (*E*,*E*,*Z*)-geranylgeranioic acid: 1.58 g, 81%; NMR δ 1.62 (s, 2 C=CMe), 1.68 (s, 2 C=CMe), 2.20 (s, C_3-Me), 5.08 (br m, 3 C=CH), 5.67 (br s, C_2-H), and 12.29 (CO_2H); IR (film) 1690 and 1645 cm^{-1}.

(10) See Experimental Section.
(11) V. D. Patil, U. R. Nayak, and S. Dev, *Tetrahedron*, **29**, 341 (1973).
(12) A. J. Birch, K. B. Chamberlain, B. P. Moore, and V. H. Powell, *Aust. J. Chem.*, **23**, 2337 (1970).

Similar treatment of (*Z,E*)-farnesylacetone (IXb) (1.77 g, 6.74 mmol) with a Wittig reagent prepared from triethyl phosphonoacetate (2.26 g, 10.1 mmol) and 50% NaH (0.42 g, 8.77 mmol) in anhydrous benzene (15 mL), followed by chromatographic purification on SiO_2 with *n*-hexane–AcOEt (40:1), afforded ethyl (*E,Z,E*)-geranylgeranioate (Xb) (1.52 g) and ethyl (*Z,Z,E*)-geranylgeranioate (0.15 g), respectively. (*E,Z,E*)-Ester Xb: mass spectrum, *m/e* 332 ($C_{22}H_{36}O_2$ requires *m/e* 332.51); NMR δ 1.25 and 4.09 (OEt), 1.60 (s, 2 C=CMe), 1.68 (s, 2 C=CMe), 2.13 (d, J = 1.4 Hz, C_3-Me), 5.08 (br m, 3 C=CH), and 5.58 (C_2-H); IR (film) 1725 and 1655 cm^{-1}. Ethyl (*Z,Z,E*)-geranylgeranioate: NMR δ 1.25 and 4.09 (OEt), 1.60 (s, 2 C=CMe), 1.69 (s, 2 C=CMe), 1.87 (d, J = 1.6 Hz, C_3-Me), 5.11 (br m, 3 C=CH), and 5.57 (br s, C_2-H); IR (film) 1725 and 1655 cm^{-1}.

Treatment of ethyl (*E,Z,E*)-geranylgeranioate (Xb) (1.39 g) with 2 N KOH (11 mL) in dioxane (22 mL) at 85 °C for 10 h afforded, after passing through a short SiO_2 column eluted with *n*-hexane–AcOEt (10:1), the corresponding (*E,Z,E*)-geranylgeranioic acid: 1.02 g, 80%; NMR δ 1.62 (s, 2 C=CMe), 1.70 (2 C=CMe), 2.20 (C_3-Me), 5.11 (br m, 3 C=CH), 5.69 (br s, C_2-H), and 12.22 (br s, CO_2H); IR (film) 1690 and 1645 cm^{-1}.

Cyclization of (*E,Z,E*)- and (*E,E,Z*)-Geranylgeranioic Acid Chlorides (Ib and Ic). To a stirred mixture of (*E,Z,E*)-geranylgeranioic acid (215 mg, 0.706 mmol) and pyridine (55.8 mg, 0.706 mmol) in anhydrous benzene (5 mL) was added $SOCl_2$ (416 mg, 3.5 mmol) at 0 °C. After 1.5 h, the resultant precipitate (pyridine hydrochloride) was removed by decantation and the volatile materials were evaporated to get crude acid chloride, which was used without any purification. An anhydrous CH_2Cl_2 (141 mL) solution of the whole amount of the crude acid chloride Ib was cooled to −78 °C under a nitrogen atmosphere, and $SnCl_4$ (61 mg, 0.235 mmol) in CH_2Cl_2 (5 mL) was added dropwise during 5 min at −78 °C. After 30 min, the reaction mixture was poured into 7% aqueous $NaHCO_3$ solution and shaken vigorously. Water was added to dissolve the formed ice and the CH_2Cl_2 layer was successively washed with aqueous 7% $NaHCO_3$ and aqueous NaCl solutions and dried over Na_2SO_4. The solvent was evaporated and the resultant residue was passed through a SiO_2 column with *n*-hexane–benzene (1:1) to give (*E,Z,E*)-chloro ketone IIb (145 mg, 64%), mp 69–70 °C from EtOH, and its dehydrochlorinated isopropenyl ketone IIIb (25 mg, 12%), oil. (*E,Z,E*)-Chloro ketone IIb: NMR δ 1.57 (sh s, $CClMe_2$), 1.52 and 1.69 (s, each 3 H, C=CMe), 2.03 (C_3-Me), 4.7–5.2 (br m, 2 C=CH), and 6.12 (br s, C_2-H). Anal. Calcd for $C_{20}H_{31}ClO$: C, 74.39; H, 9.68. Found: C, 74.54; H, 9.77.

By action of $SOCl_2$ (500 mg) and pyridine (66.3 mg) in benzene (5 mL), (*E,E,Z*)-geranylgeranioic acid (255 mg) was similarly converted into the corresponding acid chloride Ic, which was treated with $SnCl_4$ (73 mg, 0.279 mmol) in CH_2Cl_2 (168 mL) at −78 °C for 30 min to obtain (*E,E,Z*)-chloro ketone IIc (194 mg, 72%) and its dehydrochlorinated isopropenyl ketone IIIc (19.4 mg, 8%), after separation by SiO_2 column chromatography with *n*-hexane–benzene (1:1). (*E,E,Z*)-Chloro ketone IIc: mass spectrum, *m/e* 322 and 324 (M^+); NMR δ 1.57 (sh s, $CClMe_2$), 1.66 and 1.68 (each 3 H, s, C=CMe), 2.09 (d, J = 1.4 Hz, C_3-Me), 4.7–5.3 (br m, 2 C=CH), and 5.99 (br s, C_2-H). Anal. Calcd for $C_{20}H_{31}ClO$: C, 74.39; H, 9.68. Found: C, 74.30; H, 9.66.

Dehydrochlorination of Chloro Ketones IIb and IIc. A stirred mixture of (*E,Z,E*)-chloro ketone IIb (491 mg, 1.52 mmol), LiBr (396 mg, 4.56 mmol), and Li_2CO_3 (337 mg, 4.56 mmol) in dimethylformamide (20 mL) was warmed at 105 °C for 24 h under a nitrogen atmosphere, poured into water, and extracted with ether. The ether-soluble materials were passed through a SiO_2 column with *n*-hexane–benzene (1:1) to obtain the dehydrochlorinated isopropenyl ketone IIIb (313 mg, 72%) and the isomeric isopropylidene ketone XIb (36 mg, 8%), respectively. (*E,Z,E*)-Isopropenyl ketone IIIb: oil; mass spectrum, *m/e* 286 (M^+); NMR δ 1.56 (3 H) and 1.68 (6 H) (C=CMe), 2.03 (s, C_3-Me), 4.79 (C=CH_2), 4.6–5.3 (2 C=CH), and 5.93 (br s, C_2-H); IR (film) 1690, 1630, 900, and 855 cm^{-1}. Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.86; H, 10.77. (*E,Z,E*)-Isopropylidene ketone XIb: mp 73–74 °C from MeOH; mass spectrum, *m/e* 286 (M^+); NMR δ 1.59 and 1.64 (each 3 H, C_{11}- and C_7-Me), 1.73 (sh s, C=CMe_2), 2.09 (C_3-Me), 4.99 (br m, 2 C=CH), and 6.13 (br s, C_2-H); IR (KBr) 1665, 1613, and 835 cm^{-1}. Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.62; H, 10.51.

(*E,E,Z*)-Chloro ketone IIc (575 mg, 1.78 mmol) was similarly treated with LiBr (464 mg, 5.34 mmol) and Li_2CO_3 (395 mg, 5.34 mmol) in dimethylformamide (25 mL) at 105 °C for 16 h and the products were passed through a SiO_2 column with *n*-hexane–benzene (1:1) to isolate the (*E,E,Z*)-isopropenyl ketone IIIc (234 mg, 46%) and isopropylidene ketone XIc (173 mg, 34%), respectively. (*E,E,Z*)-Isopropenyl ketone IIIc: oil; mass spectrum, *m/e* 286 (M^+); NMR δ 1.63, 1.65, and 1.67 (each 3 H, s, C_7-, C_{11}-, and C_{15}-Me), 2.05 (d, J = 1.4 Hz, C_3-Me), 2.83 (br d, J = 12 Hz, C_{14}-H), 4.83 (sh s, C=CH_2), 4.7–5.4 (br m, 2 C=CH), and 5.89 (br s, C_2-H); IR (film) 1685, 1650, 1620, 900, and 840 cm^{-1}. Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.72; H, 10.49. (*E,E,Z*)-Isopropylidene ketone XIc: mp 76–77 °C from MeOH; mass spectrum, *m/e* 286 (M^+); NMR δ 1.59 and 1.66 (each 3 H, C_7-, and C_{11}-Me), 1.76 (br s, 6 H, C=CMe_2), 2.05 (s, C_3-Me), 5.03 (br m, 2 C=CH), and 5.91 (br s, C_2-H); IR (KBr) 1665, 1645, 1610, and 850 cm^{-1}. Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.76; H, 10.67.

Reduction of Isopropenyl Ketones IIIb and IIIc. To an ice–salt cooled ether (20 mL) solution of (*E,Z,E*)-isopropenyl ketone IIIb (347 mg) was added $LiAlH_4$ (50 mg), and the mixture was stirred for 1.5 h. The reaction was quenched by adding dropwise small amounts of water and then dried over Na_2SO_4, and the ether was evaporated. The residue was passed through a SiO_2 column with *n*-hexane–AcOEt (20:1) to obtain 2,3-dihydro ketone XVIb (75 mg) as two stereoisomers from the first fraction. Continued elution gave cis alcohol IVb (R = H) (185 mg, 53%) and trans alcohol XVIIb (80 mg, 23%) from the middle and last fractions, respectively. (*E,Z,E*)-*cis*-Isopropenyl alcohol IVb (R = H): mass spectrum, *m/e* 288 ($C_{20}H_{30}O$ requires *m/e* 288.46); NMR δ 1.28 (br s, OH), 1.56, 1.61, 1.70, and 1.82 (each 3 H, br s, C_{11}-, C_7-, C_3-, and C_{15}-Me) (the assignment was confirmed by decoupling; i.e., irradiation at δ 5.3 (C_2-H) and 4.7 (C=CH_2) caused the increment of the height of methyl signals at 1.70 (C_3-Me) and 1.82 (C_{15}-Me), respectively), 4.34 (br d, J = 7 Hz, C_1-H), 4.76 (br s), and 4.87 (each 1 H, C=CH_2), 4.6–5.3 (m, C_6- and C_{10}-H), and 5.34 (br d, J = 7 Hz, C_2-H); IR (film) 3400, 1660, 1640, and 890 cm^{-1}. (*E,Z,E*)-*trans*-Isopropenyl alcohol XVIIb: oil; mass spectrum, *m/e* 288 ($C_{20}H_{30}O$ requires *m/e* 288.46); NMR δ 1.33 (br s, OH), 1.56, 1.61, 1.75, and 1.77 (each 3 H, s, C_{11}-, C_7-, C_3- and C_{15}-Me), 4.14 (t, J = 9 Hz, C_1-H), 4.81 and 4.95 (each 1 H, C=CH_2), 4.6–5.2 (m, 2 C=CH), and 5.16 (br d, J = 9 Hz, C_2-H); IR (film) 3430, 1666, 1645, and 890 cm^{-1}.

(*E,E,Z*)-Isopropenyl ketone IIIc (234 mg) in ether (16 mL) was similarly treated with $LiAlH_4$ (50 mg) under ice–salt cooling and the resultant reduction products were passed through a SiO_2 column eluted with *n*-hexane–AcOEt (10:1) to give (*E,E,Z*)-cis alcohol IVc (R = H) (186 mg) and -trans alcohol XVIIc (46 mg), respectively; mass spectrum of IVc (R = H) and XVIIc, *m/e* 288 ($C_{20}H_{30}O$ requires *m/e* 288.46). (*E,E,Z*)-*cis*-Isopropenyl alcohol IVc (R = H): NMR δ 1.44 (br s, OH), 1.62 (br s, 9 H, C_3-, C_7-, and C_{11}-Me), 1.85 (s, C_{15}-Me), 4.35 (dd, J = 2 and 7 Hz, C_1-H), 4.83 and 5.00 (C=CH_2), 4.7–5.3 (m, 2 C=CH), and 5.21 (br d, J = 7 Hz, C_2-H); IR (film) 3400, 1667, 1642, 890, and 840 cm^{-1}. (*E,E,Z*)-*trans*-Isopropenyl alcohol XVIIc: NMR δ 1.40 (s, OH), 1.56 (C_7-Me), 1.63 (6 H, C_3- and C_{11}-Me), 1.72 (C_{15}-Me), 3.97 (t, J = 9 Hz, C_1-H), 4.87 and 4.95 (each 1 H, C=CH_2), 4.7–5.2 (3 C=CH); IR (film) 3400, 1665, 1643, 890, and 835 cm^{-1}.

Preparation of (*E,Z,E*)- and (*E,E,Z*)-Neocembrenes (Vb and Vc). A mixture of (*E,Z,E*)-*cis*-isopropenyl alcohol IVb (R = H) (161 mg), pyridine (4 mL), and acetic anhydride (2 mL) was kept at room temperature overnight, poured into ice water, and extracted with ether. The ether solution was successively washed with aqueous $CuSO_4$ and then aqueous NaCl solutions and dried over Na_2SO_4, and the solvent removed to give the corresponding acetate IVb (R = Ac) (175 mg) as an oil. The analytical specimen was obtained by passing the solution through a SiO_2 column with *n*-hexane–AcOEt (20:1): mass spectrum, *m/e* 330 (M^+); NMR δ 1.58 and 1.60 (each 3 H, C_7- and C_{11}-Me), 1.74 (C_{15}-Me), 1.76 (C_3-Me), 1.93 (sh s, OAc), 4.68 and 4.80 (C=CH_2), 4.7–5.3 (2 C=CH), 5.22 (br d, J = 8 Hz, C_2-H), and 5.59 (dd, J = 2.6 and 8.0 Hz, C_1-H) (the assignment was partially confirmed by a decoupling experiment; irradiation at δ 5.2 (C_2-H) and 4.7 (C=CH_2) caused the increment of the height of methyl signals at δ 1.76 (C_3-Me) and 1.74 (C_{15}-Me), respectively); IR (film) 1736, 1665, 1643, and 895 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37.

Found: C, 79.75; H, 10.30.

To an ethylamine (10 mL) solution of the (*E,Z,E*)-acetate IVb (R = Ac) (99 mg) was added Li (50 mg) at −78 °C under a nitrogen atmosphere. After 1 h, NH_4Cl (1 g) was added, ethylamine was evaporated, and the residue was taken into ether. From the ether solution was obtained (*E,Z,E*)-neocembrene (Vb) (35 mg, 43%) after passing through a SiO_2 column with *n*-hexane. (*E,Z,E*)-Neocembrene (Vb): mass spectrum, *m/e* 272 ($C_{20}H_{32}$ requires *m/e* 272.46); NMR δ 1.58 (br s, 6 H, C_3- and C_{11}-Me), 1.67 (br s, 6 H, C_7- and C_{15}-Me), 4.67 (br s, C=CH_2), and 4.7-5.3 (3 C=CH); IR (film) 1660, 1642, and 890 cm^{-1}.

Similar treatment of (*E,E,Z*)-*cis*-isopropenyl alcohol IVc (R = H) (176 mg) with acetic anhydride (2 mL) and pyridine (4 mL) at room temperature overnight afforded the corresponding acetate IVc (R = Ac) (199 mg): mass spectrum, *m/e* 330 (M^+); NMR δ 1.62 (3 H), 1.68 (6 H), and 1.80 (3 H) (C=CMe), 1.93 (Ac), 4.76 and 4.92 (C=CH_2), 5.14 (br d, *J* = 8 Hz, C_2-H), 4.7-5.3 (m, 2 C=CH), and 5.57 (dd, *J* = 3 and 8 Hz, C_1-H); IR (film) 1740, 1667, 1645, and 895 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.68; H, 10.25.

To an ethylamine (15 mL) solution of the (*E,E,Z*)-*cis*-acetate IVc (R = Ac) (155 mg) was added Li (70 mg) at −78 °C under a nitrogen atmosphere. After stirring for 1.5 h at the same temperature, NH_4Cl (1.5 g) was added, ethylamine was evaporated, and the residue was extracted with *n*-hexane. The *n*-hexane soluble hydrocarbon was passed through a SiO_2 column with *n*-hexane to give (*E,E,Z*)-neocembrene (Vc): 45 mg, 35%; mass spectrum, *m/e* 272 ($C_{20}H_{32}$ requires *m/e* 272.46); NMR δ 1.57 (6 H), 1.65 (3 H), and 1.67 (3 H) (C=CMe), 4.70 (br s, C=CH_2), and 5.03 (br m, 3 C=CH); IR (film) 1645, 890, and 832 cm^{-1}.

Preparation of *d*- and *l*-(*E,E,E*)-Neocembrenes. To an ice-cooled benzene (20 mL) solution of *dl*-(*E,E,E*)-*trans*-isopropenyl alcohol[13] XX (380 mg) and pyridine (1 mL) was added *l*-menthoxyacetic acid chloride (460 mg) and the mixture was stirred for 2 h with ice cooling and then overnight at room temperature, poured into ice water, and extracted with ether. After the solution was washed with aqueous HCl, $NaHCO_3$, and NaCl solutions, and then dried over $MgSO_4$, the ether was evaporated to obtain crude ester (590 mg), which was passed through a SiO_2 column with *n*-hexane–AcOEt (20:1) to give *l*-menthoxyacetate XXI: 568 mg; mp 68–71 °C; $[\alpha]_D$ −54.4°. Anal. Calcd for $C_{32}H_{52}O_2$: C, 81.99; H, 11.18. Found: C, 81.80; H, 11.09.

Repeated recrystallization of the ester with MeOH afforded needles, mp 82–83 °C, $[\alpha]_D$ −89.0°. The optically pure ester (73 mg) in ethylamine (15 mL) was cooled to −78 °C under a nitrogen atmosphere, Li (15 mg) was added with stirring, and the mixture was kept at the same temperature until the blue color disappeared. Water was added and the mixture was extracted with ether. Volatile materials were removed and the resultant residue was passed through a 10% $AgNO_3$–SiO_2 column with *n*-hexane–ether (10:1) to obtain *d*-neocembrene (23 mg), $[\alpha]_D$ +19.5°; mass spectrum, *m/e* 272 ($C_{20}H_{32}$ requires *m/e* 272.46).

A benzene (5 mL) solution of *dl*-(*E,E,E*)-*trans*-isopropenyl alcohol XX (194 mg) and pyridine (0.5 mL) was similarly treated with *d*-methoxyacetic acid chloride (240 mg) to result in the isolation of the corresponding ester XXII (265 mg), mp 66–69 °C; $[\alpha]_D$ +53.5°. Anal. Calcd for $C_{32}H_{52}O_2$: C, 81.99; H, 11.18. Found: C, 81.75; H, 11.03.

The crude ester was repeatedly recrystallized from MeOH to get a pure specimen, needles, mp 82–83 °C; $[\alpha]_D$ +88.0°. To the pure ester (203 mg) in ethylamine (50 mL) was added Li (40 mg) under the same conditions as in the case of the *l*-ester and *l*-neocembrene (66 mg); $[\alpha]_D$ −19.0° was obtained after a pass through a 10% $AgNO_3$–SiO_2 column with *n*-hexane–ether (10:1): mass spectrum, *m/e* 272 ($C_{20}H_{32}$ requires *m/e* 272.46). *d*- and *l*-neocembrenes were superimposable with *dl*-neocembrene in their NMR and IR spectra.

Registry No. Ib, 72623-57-5; Ic, 72623-58-6; IIb, 72623-59-7; IIc, 72638-61-0; IIIb, 72623-60-0; IIIc, 72623-61-1; IVb (R = H), 72690-07-4; IVb (R = Ac), 72690-08-5; IVc (R = H), 72690-09-6; IVc (R = Ac), 72690-10-9; (+)-Va, 72691-72-6; (−)-Va, 31570-39-5; Vb, 72690-72-3; Vc, 72690-73-4; VIb, 3790-71-4; VIc, 3879-60-5; VIIc, 24163-94-8; VIIIc, 72638-62-1; IXb, 1117-51-7; IXc, 3953-35-3; Xb, 64759-50-8; Xc, 72638-63-2; XIb, 72638-64-3; XIc, 72638-65-4; XVIb, isomer 1, 72638-66-5; XVIb, isomer 2, 72638-67-6; XVIIb, 72690-74-5; XVIIc, 72690-75-6; (±)-XX, 59686-17-8; (−)-XXI, 72638-68-7; (+)-XXII, 72690-76-7; ethyl acetoacetate, 141-97-9; ethyl (*Z,E,Z*)-geranylgeranioate, 72638-69-8; (*E,E,Z*)-geranylgeranioic acid, 72638-70-1; ethyl (*Z,Z,E*)-geranylgeranioate, 64759-49-5; (*E,Z,E*)-geranylgeranioic acid, 72638-71-2.

(13) Preparation of XX is described in ref 4.

Thienamycin Total Synthesis. 1. Synthesis of Azetidinone Precursors of (±)-Thienamycin and Its Stereoisomers

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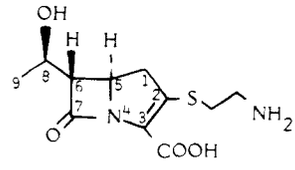
The synthesis of fully functionalized azetidinone precursors to (±)-thienamycin and its C(6)–C(8) stereoisomers is described. Cycloaddition of chlorosulfonyl isocyanate and 1-acetoxybutadiene afforded azetidinone 7 which, after appropriate modification, was hydroxyethylated via an aldol condensation, generating all four side-chain diastereomers, **11a-d**. Three of the four diastereomers were obtained in sufficient amounts for subsequent conversion to azetidinones **16a-c**, fully functionalized for elaboration to the bicyclic system.

Thienamycin (1) is an exceptionally potent, broad-spectrum β-lactam antibiotic particularly notable for its activity against *Pseudomonas* spp. and its resistance to bacterial β-lactamases. Its discovery, isolation, and structure elucidation have been the subject of previous communications from these laboratories.[1a,b] Recently we reported the total synthesis of (±)-thienamycin.[2] This and the following two papers are a full description of that work.

The absolute stereochemistry of thienamycin (1) is 5*R*,6*S*,8*R*.[1b] The novelty of the thienamycin structure can



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5R, 6S, 8R

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