

The reported method should allow versatile access to many B,C,D-ring-modified steroids which are presently inaccessible. Moreover, it employs a transition-metal complex in a step that generates the first chiral center in the target natural product, suggesting future experiments aimed at utilizing optically active metal systems to obtain

enantioselectivity. This prospect is under active scrutiny.

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Diels-Alder Reactions of Piperylenes

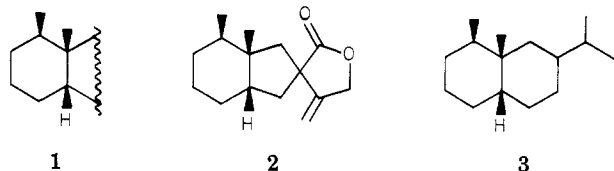
Timothy J. Brocksom*[†] and Mauricio G. Constantino[‡]

Departamento de Quimica, UFSCar, Caixa Postal 676, 13.560 São Carlos SP, Brazil, and Instituto de Quimica, USP, Caixa Postal 20.780 São Paulo SP, Brazil

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The synthesis of bakkenolide (2) and eremophilane (3) sesquiterpenes entails the construction of a *cis*-1,2-dimethylcyclohexane unit, 1, which can be synthesized by Diels-Alder reaction of *cis*-piperylene (4) and citraconic anhydride (5a). The use of a cuprous chloride/ammonium chloride catalyst led to very low yields of the desired adduct 7a together with the other structural and stereoisomers (8a-10a), which made this route impractical. However, as part of a more general study we have compared the reactions of *cis*- and *trans*-piperylene (6) with five different maleic and citraconic dienophiles, 5a-e, and obtained reasonable yields of the adducts 7c and 7d directly, thus demonstrating the utility of the CuCl/NH₄Cl catalyst for sensitive dienes. The adducts 7a-10a were transformed separately into the corresponding dimethyl esters 12-15 and then analyzed by NMR spectroscopy, which permitted the definition of their relative configurations and preferred conformations.

In our synthetic work on bakkenolide (2) and eremophilane (3) sesquiterpenes we have proposed¹ the preparation of a *cis*-1,2-dimethylcyclohexane unit, 1, as a possible



common intermediate. One approach would involve a Diels-Alder reaction² between *cis*-piperylene (4) and citraconic anhydride (5a) or *N*-phenylcitraconimide (5b). However, *cis*-piperylene (4) is known²⁻⁶ to be very unreactive to cycloaddition under the conditions usually employed. Therefore, we initiated our study using the more reactive dienophiles maleic anhydride (5c) and *N*-phenylmaleimide (5d) in the presence of catalysts and then compared the reactions of the dienophiles 5a-e with both *cis*-piperylene (4) and *trans*-piperylene (6). Fleming and Murray⁷ have described the use of 2*H*-thiopyran (11) as a substitute for *cis*-piperylene (4) in reaction with maleic dienophiles 5c and 5d. As we obtained the pure adduct 7d in 35% yield and the adduct 7c in 49% yield (together with its epimer 9c) directly from simple starting materials, we are prompted to report these and other related results.

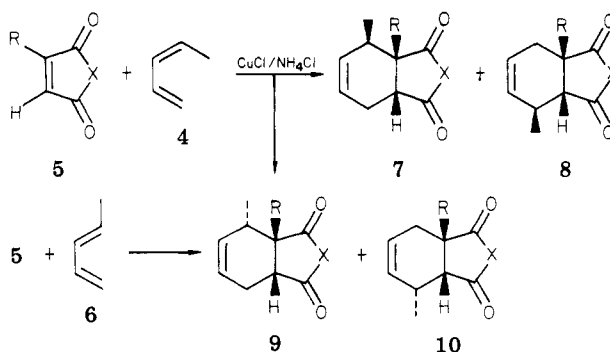
Results and Discussion

cis-Piperylene (4) is very prone to self polymerization and copolymerization with dienophiles. In our hands anhydrous aluminium chloride² only increases the polym-

Table I. Reactions of Piperylenes with Dienophiles 5a-e

diene	dieno- phile	products (yields, %)
6	5c	9c (81)
6	5d	9d (71)
4	5c	7c (49), 9c (9)
4	5d	7d (35)
6	5a	9a (67), 10a (26)
4	5a	9a (14), 10a (7), 7a (3), 8a (3.5)
6	5b	very slow reaction
6	5e	9e/10e (~3:1)
4	5e	9e + 10e + 7e + 8e

Scheme I^a



^a a, R = CH₃, X = O; b, R = CH₃, X = NPh; c, R = H, X = O; d, R = H, X = NPh; e, R = CH₂Cl, X = O.

erization rate at the expense of Diels-Alder reaction, as shown by the rapid formation of dark tars. On the other

[†]UFSCar.

[‡]USP.

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Table II. Chemical Shift Data of Dimethyl Esters 12–15

proton	chemical shift, δ			
	12	13	14	15
a	2.7–3.2 (m)	2.55–3.0 (m)	2.0–2.3 (m)	2.4–2.8 (m)
b	5.30–5.54 (m)	5.45 } (m, 2 H)	5.3–5.5 (m)	5.25–5.5 (m)
c	5.50–5.84 (m)	5.75 }	5.6–5.85 (m)	5.6–5.85 (m)
d	2.52 (m)	2.35–2.7 (m)	2.2–2.5 (m)	1.8–2.2 (m)
e	2.28 (m)	1.8–2.15 (m)	2.6–3.0 (m)	2.8–3.1 (m)
f	2.97 (dd)	2.25 (d)	2.58 (d)	2.90 (d)
<i>t</i> -CH ₃	1.16 (s)	1.30 (s)	1.28 (s)	1.26 (s)
<i>sec</i> -CH ₃	1.06 (d)	1.04 (d)	0.97 (d)	1.05 (d)
O-CH ₃	3.64, 3.70 (2 s)	3.66, 3.70 (2 s)	3.68 (s)	3.62, 3.66 (2 s)

hand, a mixture of cuprous chloride and ammonium chloride proved to be a much better Diels–Alder catalyst^{2,8} and gave reasonable yields of adducts. Table I presents our results on the noncatalyzed reactions with *trans*-piperylene (6) and the CuCl/NH₄Cl-catalyzed reactions of *cis*-piperylene (4).

The products of the reactions with maleic dienophiles 5c and 5d were easily identified by comparison of the reactions with *cis*- and *trans*-piperylenes. However, with citraconic dienophiles 5a and 5b, four distinct products are possible in each case, although *trans*-piperylene only leads to the 9 and 10 series whereas *cis*-piperylene really gives all four (7–10, Scheme I). Comparison of the easily predictable major and minor products with *trans*-piperylene (9a and 10a, respectively) and the products obtained with *cis*-piperylene (7a–10a) permitted structural identifications which we also confirmed by preparative GC separation, recrystallization of the corresponding diacids, and NMR analysis of their dimethyl esters.

Thus *cis*-piperylene (4) and maleic anhydride (5c) gave the expected adduct 7c in 49% isolated yield, together with 9% of the epimeric adduct 9c expected from *trans*-piperylene (6). Control experiments showed that *cis*-piperylene (4) can isomerize to *trans*-piperylene (6) under the reaction conditions, but the catalyst CuCl/NH₄Cl is not responsible for this. Probably traces of maleic acid present in the anhydride cause this isomerization.⁹ In support of this, *N*-phenylmaleimide 5d gave cleanly the expected adduct 7d in 35% isolated yield, while none of the epimeric adduct 9d could be observed in the rest of the crude product. These two reactions of *cis*-piperylene (4) with maleic dienophiles 5c and 5d demonstrate clearly the utility of the CuCl/NH₄Cl catalyst in Diels–Alder reactions of easily polymerizable dienes.

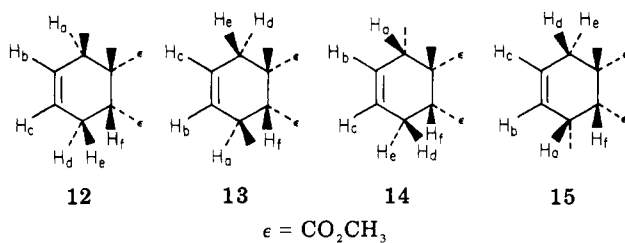
cis-Piperylene (4) and citraconic anhydride (5a) gave all four adducts with predominance of the adducts expected from *trans*-piperylene (6). The desired adduct 7a was obtained in very low yield (3%) as was the regioisomer 8a. Initial experiments with *N*-phenylcitraconimide (5b) and *trans*-piperylene (6) indicated lower reactivity compared with the anhydride 5a and led us to abandon this dienophile. Similarly, qualitative experiments with (chloromethyl)maleic anhydride (5e) demonstrated its reactivity as intermediate between the maleic (5c) and citraconic (5a) anhydrides. The products with *trans*-piperylene (6) were used as controls and indicated the formation of very low

Table III. Coupling Constants of the Adducts 12–15

protons	J_{H-H} , Hz			
	12	13	14	15
a-CH ₃	7	7	7.5	7.5
a-b	2			
a-c	2		2	2.5
a-d	5	2	7	1.5
a-e	3	3		
a-f		9		6
b-c	10		9.5	10
b-d				1.5
c-d	3.5		5	4.5
c-e	2.5		2	2.5
d-e	18.5	17	18	18
d-f	3		0	
e-f	6		10	

yields of the desired adduct 7e (plus 8e) on reaction with *cis*-piperylene (4). Also the proportion 7e + 8e/9e + 10e was smaller than that with citraconic anhydride (7a + 8a/9a + 10a).

Structural identification of 7a–10a was performed by NMR analysis of the corresponding dimethyl esters 12–15.



Extensive spin-decoupling experiments enabled us to attribute all of the proton signals and to determine a large number of the coupling constants, as presented in Tables II and III. The cited $^5J_{H_a-H_d}$ homoallylic coupling constants for compounds 12 and 14 are higher than usual (normal range 0–3 Hz), being the experimentally observed distances between the appropriate lines. However, the protons H_a, H_d, and H_e are part of a very complex spin system in which it may not be justified to obtain these coupling constants by direct measurements.¹⁰

Thus, the use of the CuCl–NH₄Cl catalyst permits the direct preparation from commercial starting materials of adducts 7c and 7d in quite reasonable yields. The adducts 7a,b,e are formed in such low yields as to be uninteresting for synthesis of bakkenolide and eremophilane sesquiterpenes, although the simplicity of their preparation might warrant further investigation for stereochemical studies. Surprisingly, the *N*-phenyl imides are less reactive than the corresponding anhydrides although earlier reports indicate the opposite.^{7,11} Our conclusions are based on

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six of the reactions cited in Table I where we could make reasonably direct comparisons (first and second, third and fourth, and fifth and seventh reactions). In each of the three comparisons the *N*-phenyl imide gave lower yields of adducts even with much longer reaction times. However, the possibility of product decomposition on long-term heating prompted us to perform a more direct comparison. Two parallel reactions were carried out with *trans*-piperylene (6) in benzene and maleic anhydride (5c) or *N*-phenylmaleimide (5d), as described in the Experimental Section. The two reaction mixtures were heated simultaneously for 10 min, cooled rapidly, isolated, and analyzed by NMR comparison of the ratio of product (9c or 9d) to starting dienophile (5c or 5d). We observed a 3:1 ratio of 9c/5c in the case of maleic anhydride whereas *N*-phenylmaleimide gave only a 1.9:1 ratio of 9d/5d. Finally, the NMR data are indicative of preferred conformations where the secondary methyl group is in the pseudoequatorial orientation in all four of the compounds 12–15. The ³J coupling constant between one olefinic proton and the neighboring methine or methylene protons depends on the dihedral angle, and Garbisch¹² has developed a simple rule for this situation. The equatorial allylic proton–olefinic proton coupling constant is 3–5 Hz whereas the axial proton gives a much smaller value of 0–2 Hz. Application of this to compounds 12–15 led to the above conclusion as regards to the preferred conformations, which for compounds 13–15 are predicted over the other possible conformations which have 1,3-diaxial interactions. However, diester 12 would seem to have no obvious preference for the indicated conformation.

Experimental Section

Melting points were determined on a Reichert Kofler block melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on Perkin-Elmer 457 or Infracord spectrometers, and nuclear magnetic resonance (NMR) spectra were recorded at 60 MHz (Varian T-60) or 100 MHz (Varian XL-100). Chemical shifts are reported in parts per million (δ) relative to Me₄Si as an internal standard, with conventional nomenclature for splitting and coupling constants. Mass spectra were recorded on Varian CH7 or CH5 spectrometers. Microanalyses were performed in the Microanalytical Laboratory, IQ-USP, Brazil, and Anorg.-Chem. Institut, Munchen, West Germany. Analytical and preparative gas chromatography separations were performed on a Varian 2868 gas chromatograph.

Maleic Anhydride–*trans*-Piperylene Adduct. *cis*-3-Methylcyclohex-4-ene-*cis*-1,2-dicarboxylic Anhydride (9c). A solution of maleic anhydride (1.96 g, 20 mmol) and *trans*-piperylene (2.72 g, 40 mmol) in benzene (20 mL) was refluxed for 30 min. The solvent was evaporated and the crystalline product (100% yield) recrystallized from cyclohexane and benzene to give 2.68 g (81%) of 9c: mp 59–61 °C (lit.¹³ mp 61 °C). Hydrolysis of a small amount of the product led to the corresponding diacid, mp 150–153 °C (lit.³ mp 156–158 °C).

***N*-Phenylmaleimide–*trans*-Piperylene Adduct. *cis*-3-Methyl-*N*-phenylcyclohex-4-ene-*cis*-1,2-dicarboximide (9d).** A solution of *N*-phenylmaleimide (173 mg, 1.0 mmol) and *trans*-piperylene (200 mg, 2.9 mmol) in benzene (2 mL) was refluxed for 1 h. The solvent was evaporated and the crystalline product (mp 112–116 °C; 100% yield) recrystallized from a 2:1 mixture of water and ethanol (6 mL) to give, from 100 mg of crude product, 71 mg (71%) of 9d: mp 114–121 °C (lit.⁷ mp 116.5–117 °C); IR (Nujol) 1700, 1200 cm⁻¹; ¹H NMR (CDCl₃) 7.1–7.7 (m, 5 H), 5.7–6.2 (m, 2 H), 3.1–3.4 (m, 2 H), 2.0–3.1 (m, 3 H) 1.40 (d, 3 H, *J* = 7.5 Hz). Anal. Calcd for C₁₅H₁₅NO₂: C, 74.67; H, 6.27;

N, 5.80. Found: C, 74.25; H, 6.17; N, 6.00.

Cuprous Chloride–Ammonium Chloride Catalyst. Cuprous chloride (16 g) was melted, the heat source was withdrawn, and ammonium chloride (9 g) was added with stirring until the mixture solidified. The product was ground quickly and sieved, and the powder smaller than 100 mesh was collected.

Maleic Anhydride–*cis*-Piperylene Adducts. *trans*-3-Methylcyclohex-4-ene-*cis*-1,2-dicarboxylic Anhydride (7c) and 9c. A mixture of maleic anhydride (980 mg, 10 mmol), *cis*-piperylene (2.72 g, 40 mmol), and CuCl–NH₄Cl catalyst (500 mg) was sealed in a glass ampule and heated at 130 °C for 2 h. After the tube was opened, the product was dissolved in chloroform, the mixture was dried with Na₂SO₄ and filtered, and the solvent was evaporated. Distillation at 100–150 °C (0.05 mm) gave 971 mg (58%) of 7c and 9c: IR (film) 1860, 1780, 1220, 925 cm⁻¹; ¹H NMR (CDCl₃) 5.8–6.0 (m, 2 H), 2.0–3.6 (m, 5 H), 1.30 (d, 3 H, *J* = 7 Hz); mass spectrum, *m/e* (relative intensity) 138 (M⁺ – 28, 21), 94 (42), 93 (45), 91 (13), 85 (13), 83 (20), 79 (100), 77 (31). GLC on a OV-17 column at 170 °C demonstrated the presence of 84% 7c (49% yield) and 16% 9c (9% yield) in the order of elution. A small amount of the crude product was hydrolyzed, and the diacid corresponding to anhydride 7c was purified by recrystallization: mp 160–162 °C (lit.³ mp 161–162 °C); mmp (of the diacids corresponding to 7c and 9c) 119–122 °C.

***N*-Phenylmaleimide–*cis*-Piperylene Adduct. *trans*-3-Methyl-*N*-phenylcyclohex-4-ene-*cis*-1,2-dicarboximide (7d).** A mixture of *N*-phenylmaleimide (173 mg, 1.0 mmol), *cis*-piperylene (272 mg, 4.0 mmol), and CuCl–NH₄Cl catalyst (50 mg) was sealed in a glass ampule and heated at 130 °C for 13 h. After the ampule was opened, the product was extracted with chloroform, diethyl ether was added to precipitate polymers, and the mixture was dried with MgSO₄ and filtered through Celite. The solvent was evaporated, and the solid product (78% yield) was recrystallized from a 2:1 mixture of water and ethanol (13 mL) to give 85 mg (35%) of 7d: mp 98–101 °C; IR (Nujol) 1700, 1190 cm⁻¹; ¹H NMR (CDCl₃) 6.9–7.3 (m, 5 H), 5.6–6.1 (m, 2 H), 1.5–3.3 (m, 5 H), 1.30 (d, 3 H, *J* = 7 Hz); mmp (7d and 9d) 86–96 °C. Anal. Calcd for C₁₅H₁₅NO₂: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.25; H, 6.40; N, 6.03.

Citraconic Anhydride–*trans*-Piperylene Adducts. 2-Methyl-*cis*-3-methylcyclohex-4-ene-*cis*-1,2-dicarboxylic Anhydride (9a) and 1-Methyl-*cis*-3-methylcyclohex-4-ene-*cis*-1,2-dicarboxylic Anhydride (10a). A solution of citraconic anhydride (2.24 g, 20 mmol), *trans*-piperylene (2.72 g, 40 mmol), and picric acid (10 mg) in benzene (10 mL) was refluxed for 48 h. The solvent and excess reagents were evaporated, and the products were distilled at 70–100 °C (0.25 mm) [lit.¹¹ bp 137 °C (10 mm)] to give 2.98 g of a citraconic anhydride, 9a, and 10a mixture. NMR and GLC (OV-17 column at 170 °C) analyses indicated the following molar percentages: citraconic anhydride, 35; 10a, 18; 9a, 47 (in the GLC elution order). Discounting recovered starting material, the yields of 10a and 9a are respectively 26% and 67%. A small amount of the crude product was hydrolyzed and recrystallized three times from water to give the corresponding diacid of 9a; mp 189–190 °C (lit.¹⁴ mp 187–188 °C). The pure diacid (100 mg, 0.50 mmol) was treated with acetic anhydride (5 mL), and then acetic acid and excess acetic anhydride were removed by distillation, and the residue was distilled at 130 °C (2 mm) to give 79.4 mg (88%) of 9a: IR (film) 1840, 1775, 1215, 960 cm⁻¹; ¹H NMR (CDCl₃) 5.6–6.1 (m, 2 H), 2.98 (dd, 1 H, *J* = 7.5, 3 Hz), 2.0–2.9 (m, 3 H), 1.48 (s, 3 H), 1.22 (d, 3 H, *J* = 7.5 Hz).

Citraconic Anhydride–*cis*-Piperylene Adducts. 2-Methyl-*trans*-3-methylcyclohex-4-ene-*cis*-1,2-dicarboxylic Anhydride (7a), 1-Methyl-*trans*-3-methylcyclohex-4-ene-*cis*-1,2-dicarboxylic Anhydride (8a), 9a, and 10a. A mixture of citraconic anhydride (11.2 g, 100 mmol), *cis*-piperylene (27.2 g, 400 mmol), and CuCl–NH₄Cl catalyst (5 g) was sealed in a glass ampule and heated at 200 °C for 45 min. The product was dissolved in chloroform, the mixture filtered, and the solvent evaporated. The product was redissolved in chloroform (50 mL), and diethyl ether (250 mL) was added until no more precipitate was formed. The suspension was filtered through a MgSO₄–Celite

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pad and the solvent evaporated. The residue was distilled at 70–100 °C (0.25 mm) to give 4.90 g (27%) of a 7a–10a mixture (11%, 13%, 51%, and 25%, respectively, by GLC). Part of this material was submitted to preparative GLC on a 13% OV-17 column (20 ft × 3/8 in. Chromosorb W support) at 200 °C with a nitrogen flow of 120 mL/min. The first three products were collected separately and identified as 8a, 10a, and 9a in the order of elution. 10a: ¹H NMR (CDCl₃) 5.7–6.0 (m, 2 H), 2.88 (d, 1 H, J = 6 Hz), 1.9–3.0 (m, 3 H), 1.48 (s, 3 H), 1.43 (d, 3 H, J = 7 Hz). Each one of the three products was separately hydrolyzed and recrystallized from water, the corresponding diacids were esterified with diazomethane, and the dimethyl esters 13–15 were distilled. The NMR data for each of these compounds and compound 12 can be found in Tables II and III.

13: IR (film) 1735, 1205 cm⁻¹; mass spectrum, *m/e* (relative intensity) 226 (2), 195 (8), 194 (7), 166 (31), 107 (100). Anal. Calcd for C₁₂H₁₈O₄: C, 63.70; H, 8.02. Found: C, 63.94; H, 8.04.

14: IR (Nujol) 1720, 1660 cm⁻¹; mass spectrum, *m/e* (relative intensity) 226 (2), 195 (5), 194 (6), 166 (17), 107 (100).

15: IR (Nujol) 1730, 1190 cm⁻¹; mass spectrum, *m/e* (relative intensity) 226 (1), 195 (6), 194 (7), 166 (27), 107 (100).

Part of the initial mixture of anhydrides was hydrolyzed, recrystallized from water, and esterified with diazomethane. This product mixture was submitted to preparative GLC on a 13% OV-17 column (20 ft × 3/8 in. Chromosorb W support) at 220 °C with a nitrogen flow of 120 mL/min. The fourth peak was collected and distilled at 80–90 °C (0.25 mm) to give 12; IR (film) 1730, 1200 cm⁻¹; mass spectrum, *m/e* (relative intensity) 226 (2), 195 (6), 194 (7), 166 (28), 107 (100). Anal. Calcd for C₁₂H₁₈O₄: C, 63.70; H, 8.02. Found: C, 63.68; H, 8.02.

Comparative Reactions of *trans*-Piperylene with Maleic Anhydride and *N*-Phenylmaleimide. A solution of maleic anhydride (98 mg, 1 mmol) and *trans*-piperylene (136 mg, 2 mmol) in benzene (2 mL) was prepared. A separate solution of *N*-phenylmaleimide (173 mg, 1 mmol) and *trans*-piperylene (136 mg, 2 mmol) in benzene (2 mL) was also prepared at the same time. The two solutions were then immediately set up for reflux and heated simultaneously in the same preheated oil bath for 10 min. The two reaction systems were rapidly cooled to room temperature, and the benzene and excess *trans*-piperylene were removed by evaporation. The two products were dissolved in CDCl₃ and analyzed by NMR: first reaction, product (9c)/maleic anhydride (5c) ratio of 3.0:1; second reaction, product (9d)/*N*-phenylmaleimide (5d) ratio of 1.9:1.

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Silyl Phosphites. 21. A New Method for the Synthesis of L-Ascorbic Acid 2-O-Phosphate¹ by Utilizing Phosphoryl Rearrangement

Mitsuo Sekine, Tetsuaki Futatsugi, and Tsujiaki Hata*

Department of Life Chemistry, Nagatsuta, Midoriku, Yokohama 227, Japan

Friedrich Cramer

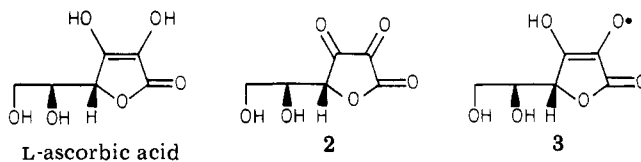
Abteilung Chemie, Max-Planck-Institut für Experimentelle Medizin, 3400 Göttingen, FRG

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A stabilized form of vitamin C, L-ascorbic acid 2-O-phosphate (1), was successfully synthesized by a new method via a fully trimethylsilylated L-ascorbic acid (4) that was prepared in high yield by silylation of L-ascorbic acid with hexamethyldisilazane. Bromination of 4 gave an adduct (6) that was isomerized during distillation to a trimethylsilylated bicyclic half acetal (8) of dehydroascorbic acid. Addition of tris(trimethylsilyl) phosphite (TMSP) to 8 gave carbonyl addition compounds 9a and 9b, which underwent thermal rearrangement to give a mixture of bis(trimethylsilyl)-3,5,6-tris-(O-(trimethylsilyl))-L-ascorbic acid 2-O-phosphate (10) and its 3-O-isomer 13 in the ratio of 88:12. Treatment of the mixture with cyclohexylamine in methanol gave selectively tricyclohexylammonium salt of L-ascorbic acid 2-O-phosphate in 53% yield.

L-Ascorbic acid is well-known to be susceptible toward thermal and oxidative degradation, and hence various stable derivatives of L-ascorbic acid have been searched for and prepared in a number of laboratories.^{2–10} Among

these derivatives L-ascorbic acid 2-O-phosphate (1) has the



promising property of generating antiscorbutic activity in vivo through enzymic degradation to free L-ascorbic acid. Cutolo and Larizza⁴ first reported the synthesis of 1 by the reaction of 5,6-isopropylidene-L-ascorbic acid with phos-

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