A Stereoselective Method for the Preparation of HIV-1 Protease Inhibitors Based on the Lewis Acid Mediated Reaction of Allylsilanes and *N*-Boc-α-amino Aldehydes

Fabiana D'Aniello and Maurizio Taddei*

Dipartimento di Chimica Organica "U.Schiff", Università di Firenze, Via G. Capponi 9, I-50121 Firenze, Italy

Received March 30, 1992

Among the numerous intervention points that could be exploited in development of drugs for acquired immunodeficiency syndrome (AIDS) therapy,[1] the virally encoded protease has emerged as one of the most popular targets.[2] Several potent synthetic inhibitors of this aspartyl protease have been reported to contain dipeptide mimics, known as hydroxyethylene dipeptide isosters.[3]

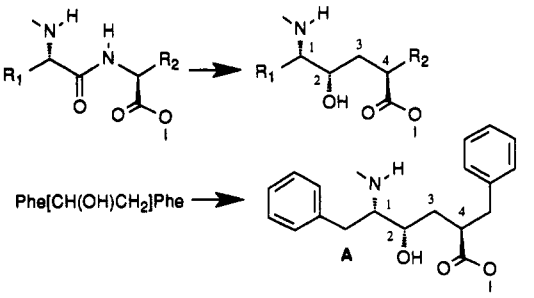
The hydroxy amino acid framework **A** in Scheme I, where the peptidic linkage of the sequence Phe-Phe is replaced by a $CH(OH)CH_2$ group, resulted as the core unit of a potent inhibitor of HIV-1 protease, and its asymmetric synthesis has been recently published.[4]

We report here our stereoselective approach for synthesizing these type of hydroxyethylene dipeptide isosters. The synthesis, which can allow the preparation of molecules of type **A** carrying different substitutents in position 4, is based on the Lewis acid mediated reaction of allylsilanes and aldehydes.[5,6]

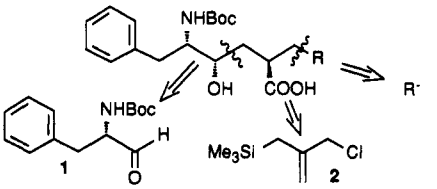
We started from *N*-Boc-phenylalaninal (**1**) prepared via the method of Feherentz and Castro.[7] The aldehyde was reacted with the commercially available 2-(chloromethyl)-3-(trimethylsilyl)-1-propene (**2**) in the presence of $BF_3{\cdot}OEt_2$ to give the amino alcohol **3** in high yield (Scheme III).

The reagents were maintained in dry chloroform[8] at −60 °C in the presence of 1.5 equiv of the Lewis acid for one night, and after hydrolytic workup, compound **3** could be isolated in high yield as a crude product which was used directly in the next step but which could be purified by column chromatography on silica gel in yields ranging from 65 to 85%. A small amount of the minor diastereoisomer (2–5%) was detected in the ^1H NMR spectrum of the crude, but it was removed during the column chromatography.

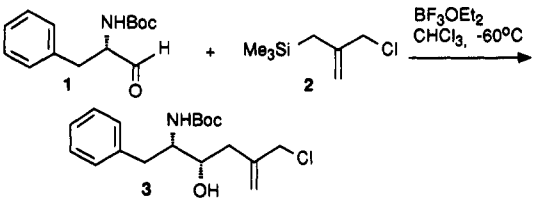
Scheme I



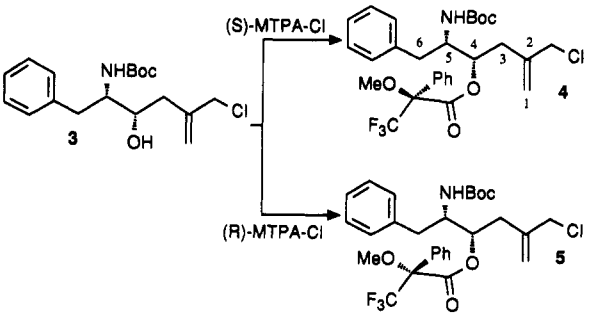
Scheme II



Scheme III



Scheme IV



Scheme V

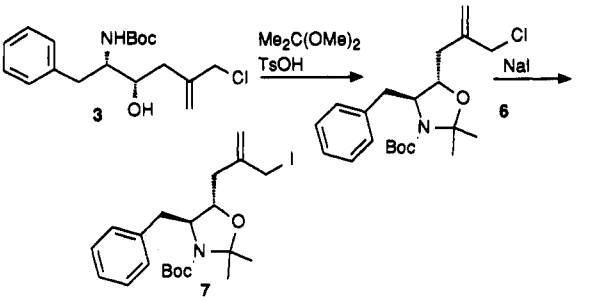


Table I. Determination of the Absolute Configuration of 3

	δ_H C(4)	δ_H C(5)	δ_H C(6)	δ_H C(3)	δ_H CH_2Cl
4 (*S*)-MTPA	5.275	4.099	2.675	2.509	3.949
5 (*R*)-MTPA	5.280	4.081	2.563	2.563	3.990
$\Delta\delta = \delta_{(S)} - \delta_{(R)}$	−0.005	0.018	0.112	−0.054	−0.041

The absolute stereochemistry (as the optical purity) of product **3** was determined by ^1H NMR analysis of the

(1) Mitsuya, H.; Yarchoan, R.; Brades, S. *Science* **1990**, *249*, 1533.

(2) (a) Darke, P. L.; Len, C.-T.; Davis, L. J.; Heimbach, J. C.; Diehl, R. E.; Hill, W. S.; Dixon, R. A. J.; Sigal, I. S. J. *J. Biol. Chem.* **1989**, *264*, 2307. (b) McQuade, T. J.; Tomasselli, A. G.; Liu, L.; Karacostas, V.; Moss, B.; Sowyer, T. K.; Heinrikson, R. L.; Torpley, W. R. *Science* **1990**, *247*, 454.

(3) (a) Rich, D. H.; Sun, C.-Q.; Vara Prasad, J. V. N.; Pathiasseril, A.; Toth, M. V.; Marshall, G. R.; Clare, M.; Mueller, R. A.; Hauseman, K. *J. Med. Chem.* **1991**, *34*, 1225. (b) Vacca, J. P.; Guare, J. P.; deSolms, S. J.; Sanders, W. M.; Giuliani, E. A.; Young, S. D.; Darke, P. L.; Zugay, J.; Sigal, I. S.; Schleif, W. A.; Quintero, J. C.; Emini, E. A.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1991**, *34*, 1222. (c) Bone, R.; Vacca, J. P.; Anderson, P. S.; Hollaway, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 9382 and references therein.

(4) Ghosh, A. K.; McKee, S. P.; Thompson, W. J. *J. Org. Chem.* **1991**, *56*, 6500.

(5) (a) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57. (b) Nativi, C.; Ricci, A.; Taddei, M. in *Frontiers of Organosilicon Chemistry*; Bassindale, A. R., Gaspar, P. P., Eds.; The Royal Society of Chemistry: Letchworth, 1991, p 332.

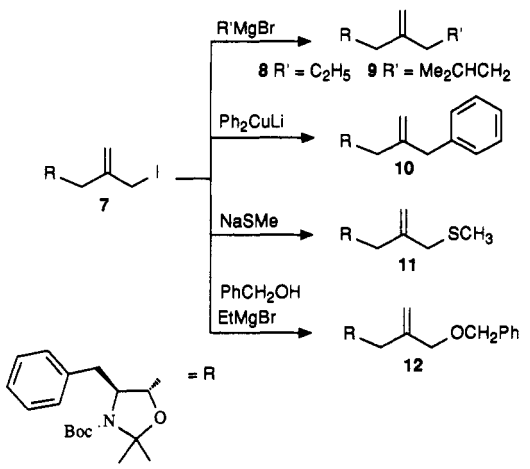
(6) Among several other syntheses of hydroxyethylene dipeptide isosters reported in the literature (see citations in ref 4) the use of allylsilanes has been previously reported: (a) Vara Prasad, J. V. N.; Rich, D. H. *Tetrahedron Lett.* **1990**, *31*, 1803. (b) Vara Prasad, J. V. N.; Rich, D. H. *Tetrahedron Lett.* **1991**, *32*, 5857.

(7) Feherentz, J. A.; Castro, B. *Synthesis* **1983**, 676.

(8) The use of $CHCl_3$ (not advisable because it is a cancer suspect agent) was determinant in the reaction. The use of CH_2Cl_2 gave much lower yields with disruption of the starting aldehyde. Moreover reaction performed in the presence of $SnCl_4$ or $TiCl_4$ gave 25–30% yield of the product of the amino aldehyde–ene reaction as described: Mikami, K.; Kaneko, M.; Loh, T.-P.; Terada, M.; Nakai, T. *Tetrahedron Lett.* **1990**, *31*, 3909.

0022-3263/92/1957-5247$03.00/0

Scheme VI



corresponding esters of the Mosher's acids (*R*)-MTPA and (*S*)-MTPA (Scheme IV). We compared the spectra of compounds **4** and **5**, and the observation of the differences in the chemical shifts reported in Table I suggested[9] the attribution of the *S* configuration at C-4.

Products **4** and **5** were submitted also to GC analysis and showed a single peak, which indicated that the products were enantiomerically pure, providing that the starting aldehyde **1** should be used "freshly prepared". When we used, in the preparation of **3**, an aldehyde kept for 1 week in a refrigerator, product **4** or **5** resulted, upon GC analysis, as a mixture of two isomers in an approximately 4:1 ratio, suggesting a possible racemization of the starting aldehyde during the storage.

Compound **3** was then protected as the 1,3-oxazolidine **6** ($Me_2C(OMe)_2$, TsOH, rt, 24 h, 84% yield), and the allylic chloride was transformed into the corresponding iodide **7** (dry NaI, acetone, rt, 24 h, 88% yield) (Scheme V).

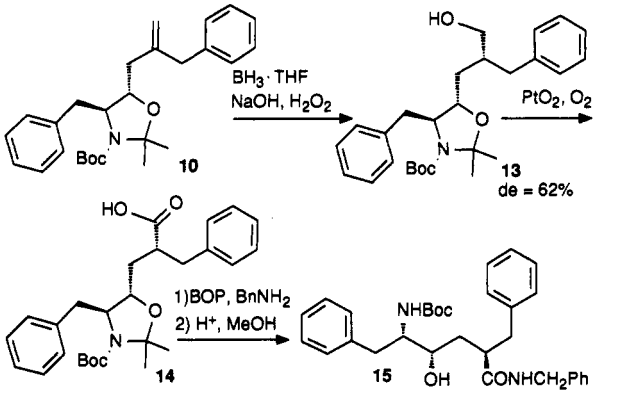
Finally the right side of the dipeptide isoster was introduced by a nucleophilic substitution of the allylic iodide with Grignard reagents (see Scheme VI) to give products **8** (45% yield) and **9** (56% yield), with cuprates to give product **10** (76% yield), and with sodium mercaptides or magnesium alkoxides to give products **11** (71% yield) or **12** (39% yield).

Product **7** resulted as a versatile intermediate for the introduction of different functional groups in position 4 of the hydroxyethylene isoster. A synthetic methodology which allows compounds with programmed variations of the substituents to be synthesized is particularly important in the screening of the pharmacological activity and in a study of structure–activity relationship directed toward the design of the best substituent for position 4.

The introduction of the COOH group on product **10** and the final preparation of the core unit of the potent HIV-1 protease inhibitor **15** is reported in Scheme VII.

Oxidative hydroboration (BH_3·THF, 0 °C, then NaOH and H_2O_2, 58% yield) gave alcohol **13** with a de of 62%. The major product was isolated by column chromatography and carried over to the next steps without investigating the stereochemistry at the newly formed stereogenic center. Oxidation with PtO_2/O_2 gave acid **14** in 62% yield. Finally the desired product **15** was prepared by condensation with benzyl amine in the presence of (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and deprotection in acidic medium (50% yield). Product **15** presented the same physical (mp

Scheme VII



179–180 °C, lit.[10] mp 179–182 °C) and spectroscopic data[10] of the product prepared by Ghosh and co-workers.

The preparation of other dipeptide isosters derived from product **7** is in progress as the tests to determinate their activity on HIV-1 protease.

Experimental Section

(4*S*,5*S*)-5-((*tert*-Butoxycarbonyl)amino)-2-(chloromethyl)-6-phenyl-1-hexen-4-ol (3). To a stirred solution of aldehyde **1** (0.70 g, 2.8 mmol) in dry chloroform (5 mL) cooled to −60 °C under nitrogen was added with a syringe boron trifluoride etherate (0.6 g, 4.2 mmol). After 5 min, a solution of allylsilane **2** (0.77 g, 4.7 mmol) in dry chloroform (3 mL) was slowly added. The reaction mixture was stirred at −60 °C for 12 h. A saturated solution of $NaHCO_3$ (3 mL) was added, followed by Et_2O (20 mL), and the mixture was warmed to room temperature with vigorous stirring. The organic layer was separated, washed with 10% NH_4Cl and brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, column chromatography on silica gel (hexane/ethyl acetate, 1/1) gave product **3** (0.8 g, 84% yield) as a dense oil which solidified on standing (mp 45–49 °C): IR (neat) ν 3350, 3030, 2980, 1700, 1610, 1485, 1020 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40 (s, 9 H, t-Bu), 2.2 (b, 1 H, OH), 2.35 (m, 2 H, CH_2C=), 2.90 (m, 2 H, CH_2Ph), 3.80 (m, 2 H, CHN and CHO), 3.98 (m, 2 H, CH_2Cl), 4.80 (bd, 1 H, NH), 5.03 (m, 1 H, CH_2=), 5.25 (m, 1 H, CH_2=), 7.2 (m, 5 H, arom.); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.8, 37.6, 37.9, 48.2, 56.4, 69.0, 79.9, 118.6, 126.9, 128.9, 129.7, 138.6, 142.1, 156.2; MS *m/e* 340 (M^+), 304, 248, 192, 164, 148, 120, 91, 57 (base).

A sample of the product was dissolved in dry benzene, the solvent was evaporated at the rotavapor, and the residue was dried overnight at 30 °C (0.02 mmHg) to give a sample which was submitted to elemental analysis. Anal. Calcd for $C_{18}H_{26}ClNO_3$: C, 63.60; H, 7.71; N, 4.12. Found: C, 64.00; H, 7.50; N, 4.20.

(*S*)-MTPA Ester of Alcohol 3 (4). Product **4** was prepared under the standard conditions (see ref 9) and purified by column chromatography on silica gel (hexane/ethyl acetate, 8/2): ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9 H, t-Bu), 2.50 (m, 2 H, CH_2C=), 2.67 (m, 2 H, CH_2Ph), 3.58 (s, 3 H, OMe), 3.95 (m, 2 H, CH_2Cl), 4.10 (m, 1 H, CHN), 4.4 (bd, 1 H, NH), 4.92 (m, 1 H, CH_2=), 5.13 (m, 1 H, CH_2=), 5.27 (m, 1 H, CHO), 7.10, 7.20, 7.35, and 7.48 (m, 10 H, arom).

(*R*)-MTPA ester of alcohol 3 (5): ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9 H, t-Bu), 2.56 (m, 4 H, CH_2C= and CH_2Ph), 3.56 (s, 3 H, OMe), 3.99 (m, 2 H, CH_2Cl), 4.08 (m, 1 H, CHN), 4.5 (bd, 1 H, NH), 4.92 (m, 1 H, CH_2=), 5.20 (m, 1 H, CH_2=), 5.28 (m, 1 H, CHO), 7.10, 7.20, 7.35, and 7.48 (m, 10 H, arom).

(4*S*,5*S*)-4-Benzyl-3-(*tert*-butoxycarbonyl)-5-(2-(chloromethyl)-3-propenyl)-2,2-dimethyl-1,3-oxazolidine (6). To a solution of the amino alcohol derivative **3** (0.76 g, 2.2 mmol) in 2,2-dimethoxyethane (3 mL), stirred at room temperature, was added *p*-toluenesulfonic acid (16 mg), and the mixture was stirred for 46 h at room temperature. Et_2O (30 mL) was added, and the organic layer was washed with 10% $NaHCO_3$. The organic layer was separated and dried over anhydrous Na_2SO_4, and after

(9) Ohtani, I.; Kusuni, T.; Koshman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092 and references therein.

(10) See the supplementary material of the paper in ref 4.

evaporation of the solvent, column chromatography on silica gel (hexane/ethyl acetate, 10/1) gave **6** (0.68 g, 84% yield) as an oil: IR (neat) ν 3010, 2960, 2950, 1705, 1590, 1450 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.52 (s, 9 H, t-Bu), 1.58 (s, 6 H, Me), 2.1 (bm, 1 H, CH_2C=), 2.2 (m, 1 H, CH_2C=), 2.7 (bm, 1 H, CH_2Ph), 3.25 (m, 1 H, CH_2Ph), 3.8 (m, 3 H, CH_2Cl and CHN), 4.05 (m, 1 H, collapsing to d by strong irradiation at 2.5 ppm, J = 5 Hz, CHO), 4.65 (m, 1 H, CH_2=), 5.03 (m, 1 H, CH_2=), 7.2 (m, 5 H, arom); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.4, 27.5, 29.0, 38.4, 38.6, 48.4, 48.8, 63.5, 80.5, 95.2, 117.5, 127.1, 130.0, 130.2, 138.1, 141.9, 153.2; MS m/e 379 (M^+), 290, 288, 232, 190, 188, 57 (base). Anal. Calcd for $C_{21}H_{30}NO_3Cl$: C, 63.39; H, 7.96; N, 3.96; O, 12.63; Cl, 9.33. Found: C, 63.89; H, 7.87; N, 3.76.

(4*S*,5*S*)-4-Benzyl-3-(*tert*-butoxycarbonyl)-5-(2-(iodomethyl)-3-propenyl)-2,2-dimethyl-1,3-oxazolidine (7). Anhydrous NaI (0.66 g, 3.2 mmol) was dispersed in acetone (3 mL), product **6** (0.5 g, 1.35 mmol) was added, and the mixture was stirred in the dark for 12 h. Et_2O (20 mL) was added, the mixture was filtered on Celite, and the residue was washed several times with Et_2O. The filtrate was concentrated, Et_2O was added to the residue, and the mixture was filtered on a small sinter. The solvent was evaporated to give **7** as a crude yellow oil (0.55 g, 88% yield) which could be purified by column chromatography on silica gel (hexane/ethyl acetate, 10/1): ^1H NMR (200 MHz, $CDCl_3$) δ 1.52 (s, 9 H, t-Bu), 1.58 (s, 6 H, Me), 2.2 (bm, 1 H, CH_2C=), 2.35 (m, 1 H, CH_2C=), 2.6 (bm, 1 H, CH_2Ph), 3.26 (m, 1 H, CH_2Ph), 3.68 (m, 2 H, CH_2I), 3.77 (m, 1 H, CHN), 4.02 (m, 1 H, CHO), 4.76 (m, 1 H, CH_2=), 5.11 (m, 1 H, CH_2=), 7.2 (m, 5 H, arom); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.0, 18.7, 24.7, 29.0, 39.5, 39.4, 48.4, 49.9, 80.5, 98.6, 116.7, 127.1, 129.9, 130.1, 138.1, 143.3, 156.8; MS m/e 471 (M^+), 400, 324, 280, 91, 57 (base). Anal. Calcd for $C_{21}H_{30}NO_3I$: C, 53.51; H, 6.41; N, 2.97; O, 10.18; I, 26.92. Found: C, 53.01; H, 6.51; N, 2.89.

(4*S*,5*S*)-4-Benzyl-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-5-(2-propyl-3-propenyl)-1,3-oxazolidine (8). A solution of ethylmagnesium bromide (0.18 mL of a 2 M solution in Et_2O, 0.36 mmol) was cooled to −78 °C, and a solution of the iodide **7** (0.1 g, 0.217 mmol) in THF (3 mL) was added with a syringe. The mixture was warmed to room temperature and stirred for an additional 30 min. Et_2O (5 mL) was added, followed by 10% NH_4Cl. After the usual workup, column chromatography on silica gel (hexane/ethyl acetate, 10/1.5) gave product **8** (36 mg, 45% yield): ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (t like, 3 H, CH_3), 1.4–1.8 (bm, 4 H, CH_2), 1.54 (s, 9 H, t-Bu), 1.60 (bs, 6 H, Me), 1.88 (m, 1 H, CH_2C=), 2.20 (m, 1 H, CH_2C=) 2.80 (m, 1 H, CH_2Ph), 3.25 (m, 1 H, CH_2Ph), 3.85 (m, 1 H, CHN), 4.05 (m, 1 H, CHO), 4.61 (m, 1 H, CH_2=), 4.71 (m, 1 H, CH_2=), 7.2 (m, 5 H, arom); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.6, 22.0, 24.4, 25.7, 29.0, 30.6, 38.6, 39.4, 46.2, 49.8, 80.0, 95.6, 118.3, 126.9, 128.9, 129.9, 138.2, 141.6, 156.0; MS m/e 373 (M^+), 358, 316, 282, 238, 91, 57(base). Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.96; H, 9.44; N, 3.75; O, 12.85. Found: C, 73.69; H, 9.55; N, 3.47.

(4*S*,5*S*)-4-Benzyl-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-5-(2-(2-methylpropyl)-3-propenyl)-1,3-oxazolidine (9). Via the same procedure described for product **8**, column chromatography on silica gel (hexane/ethyl acetate, 10/1.5) gave **9** (49 mg, 56% yield): ^1H NMR (200 MHz, $CDCl_3$) δ 0.81 (m, 6 H, CH_3 i-Pr), 1.1–1.8 (bm, 5 H, CH_2 and CH), 1.54 (s, 9 H, t-Bu), 1.60 (bs, 6 H, Me), 2.0 (m, 1 H, CH_2C=), 2.4 (m, 1 H, CH_2C=), 2.8 (m, 1 H, CH_2Ph), 3.2 (m, 1 H, CH_2Ph), 3.85 (m, 1 H, CHN), 4.02 (m of 6 lines, 1 H, CHO), 4.52 (m, 1 H, CH_2=), 4.63 (m, 1 H, CH_2=), 7.2 (m, 5 H, arom); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.7, 19.6, 24.4, 27.5, 29.0, 29.9, 30.9, 38.6, 39.4, 48.4, 48.8, 80.5, 93.6, 117.5, 127.9, 129.9, 130.1, 138.1, 141.9, 157.0; MS m/e 401 (M^+), 386, 346, 330, 254, 210, 152, 91, 57 (base). Anal. Calcd for $C_{25}H_{39}NO_3$. C, 73.17; H, 10.41; N, 3.71; O, 17.71. Found: C, 73.01; H, 10.21; N, 3.67.

(4*S*,5*S*)-4-Benzyl-5-(2-benzyl-3-propenyl)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidine (10). Copper cyanide (45 mg, 0.5 mmol) was dispersed in THF (0.5 mL), the mixture was cooled to −23 °C, and a solution of phenyllithium (0.5 mL of a 2 M solution in cyclohexane, 1 mmol) was added with a syringe. The mixture was stirred 30 min at this temperature and for 30 min at 0 °C. After the reaction mixture was cooled to −78 °C, a solution of iodide **7** (0.22 g, 0.5 mmol) in THF (2 mL) was added, and the mixture was stirred at room temperature for 1 h. After hydrolitic workup with 20% NH_3/NH_4Cl (2 mL), addition of Et_2O (5 mL), separation of the organic layer, and drying over anhydrous Na_2SO_4, column chromatography on silica gel (hexane/ethyl acetate, 4/1) gave product **10** (0.16 g, 76% yield) as a dense oil which solidified on standing: ^1H NMR (200 MHz, $CDCl_3$) δ 1.51 (s, 3 H, Me), 1.53 (s, 9 H, t-Bu), 1.58 (s, 3 H, Me), 2.0 (bm, 1 H, CH_2C=), 2.60 (m, 1 H, CH_2C=), 2.75 (m, 1 H, CH_2Ph), 3.08 (m, 2 H, CH_2Ph), 3.20 (m, 1 H, CH_2Ph), 3.81 (m, 1 H, CHN) 4.08 (m of 8 lines, 1 H, CHO), 4.70 (m, 2 H, CH_2=), 7.1 and 7.2 (m, 10 H, arom); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.4, 27.9, 29.1, 38.4, 38.6, 39.9, 48.4, 48.9, 80.2, 94.3, 117.6, 127.9, 129.8, 129.9, 130.2, 130.7, 139.7, 141.3, 141.9, 156.7; MS m/e 406 (M^+ − 15), 350, 330, 230, 91, 57. Anal. Calcd for $C_{27}H_{35}NO_3$: C, 76.92; H, 8.37; N, 3.32; O, 11.38. Found: C, 77.01; H, 8.30; N, 3.39.

(4*S*,5*S*)-4-Benzyl-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-5-(2-((methylthio)methyl)-3-propenyl)-1,3-oxazolidine (11). A mixture of iodide **7** (0.24 g, 0.55 mmol) and sodium methylmercaptide (0.38 g, 5.5 mmol) were stirred in acetone (2 mL) for 24 h at room temperature. After hydrolitic workup with Et_2O (10 mL) and saturated Na_2SO_4, column chromatography on silica gel (hexane/ethyl acetate, 10/1.5) gave product **11** (0.15 g, 71% yield): ^1H NMR (200 MHz, $CDCl_3$) δ 1.39 (s, 3 H, Me), 1.49 (s, 3 H, Me), 1.53 (s, 9 H, t-Bu), 1.84 (s, 3 H, SMe), 2.2 (bm, 1 H, CH_2C=), 2.30 (m, 1 H, CH_2C=), 2.85 (m, 3 H, CH_2S and CH_2Ph), 3.20 (m, 1 H, CH_2Ph), 3.83 (m, 1 H, CHN), 4.06 (m, 1 H, CHO), 4.65 (m, 1 H, CH_2=), 4.75 (m, 1 H, CH_2=), 7.2 (m, 5 H, arom); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.9, 27.6, 27.9, 29.0, 39.9, 40.3, 48.5, 49.6, 59.6, 80.5, 94.6, 115.6, 127.0, 129.7, 130.5, 138.3, 141.2, 156.8; MS m/e 391 (M^+), 376, 335, 318, 300, 200, 91, 57 (base). Anal. Calcd for $C_{22}H_{33}NO_3S$: C, 67.48; H, 8.49; N, 3.58; O, 12.26; S, 8.19. Found: C, 67.24; H, 8.64; N, 3.48.

(4*S*,5*S*)-4-Benzyl-5-(2-((benzyloxy)methyl)-3-propenyl)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidine (12). Benzyl alcohol (0.11 g, 1 mmol) was dissolved in THF (2 mL), the mixture was cooled to 0 °C, and ethylmagnesium bromide (0.5 mL of a 2M solution in Et_2O, 1 mmol) was added with a syringe. The mixture was warmed to room temperature and stirred 1 h. After the mixture was cooled again to 0 °C, a solution of the iodide **7** (0.24 g, 0.55 mmol) in THF (1 mL) was added, and the mixture was stirred for 24 h at room temperature. After the usual hydrolitic workup, column chromatography on silica gel (hexane/ethyl acetate, 9/1) gave product **12** (96 mg, 39% yield): ^1H NMR (200 MHz, $CDCl_3$) δ 1.32 (s, 3 H, Me), 1.52 (s, 9 H, t-Bu), 1.59 (s, 3 H, Me), 2.1 (bm, 1 H, CH_2C=), 2.25 (m, 1 H, CH_2C=), 2.75 (m, 1 H, CH_2Ph), 3.25 (m, 1 H, CH_2Ph), 3.86 (m, 1 H, CHN), 4.05 (m, 1 H, CHO), 4.1–4.9 (bm, 5 H, CH= and CH_2O), 5.10 (m, 1 H, CH_2=), 7.1, 7.2, and 7.4 (m, 10 H, arom); MS m/e 436 (M^+ − 15), 360, 336, 260, 91, 57 (base). Anal. Calcd for $C_{28}H_{37}NO_4$: C, 70.55; H, 9.52; N, 3.58; O, 16.34. Found: C, 70.32; H, 9.65; N, 3.45.

(4*S*,5*S*)-4-Benzyl-3-(*tert*-butoxycarbonyl)-5-((2*R*)-3-hydroxy-2-benzylpropyl)-2,2-dimethyl-1,3-oxazolidine (13). To a solution of product **10** (0.16 g, 0.38 mmol) in THF (1 mL), cooled to 0 °C, was added with a syringe a borane–THF complex (0.4 mL of a 1 M solution in THF, 0.4 mmol). After the mixture was stirred for 3 h at 0 °C, ethanol (0.3 mL) was added followed by NaOH (1 mL of a 3 M solution) and 30% hydrogen peroxide (0.8 mL). The mixture was stirred at rt for 4 h. Ethyl acetate (5 mL) was added, and the organic layer was separated and washed with Na_2SO_3 (10%) and brine. After drying over anhydrous Na_2SO_4 and evaporation of the solvent, column chromatography on silica gel (hexane/ethyl acetate, 2/1) gave product **13** (98 mg, 58% yield) and a minor isomer (23 mg, 14% yield). **13**: IR (neat) ν 3350, 3010, 2960, 1700, 1600, 1480 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.4–2.2 (bm, 5 H, 2 CH_2 and CH), 1.58 (bs, 15 H, t-Bu and Me), 1.9 (bs, 1 H, OH), 2.8 (m, 1 H, CH_2Ph), 3.1 (m, 1 H, CH_2Ph), 3.5 (m, 2 H, CH_2O), 3.7 (m, 1 H, CNH), 4.02 (m, 1 H, CHO), 7.0 and 7.2 (m, 10 H, arom); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.2, 27.5, 29.0, 30.1, 31.6, 34.1, 40.9, 45.7, 46.2, 63.8, 80.7, 96.4, 127.1, 128.7, 129.0, 129.5, 130.2, 131.8, 137.9, 140.5, 156.4; MS m/e 406 (M^+ − 15), 382, 345, 327, 226, 57 (base). Anal. Calcd for $C_{27}H_{37}NO_4$: C, 73.77; H, 8.48; N, 3.19; O, 14.56. Found: C, 73.57; H, 8.74; N, 3.11.

Minor isomer: ^1H NMR (200 MHz, $CDCl_3$) δ 1.4–2.2 (bm, 5 H, 2 CH_2 and CH), 1.50 (bs, 15 H, t-Bu and Me), 1.9 (bs, 1 H, OH), 2.8 (m, 1 H, CH_2Ph), 3.3 (m, 1 H, CH_2Ph), 3.5 (m, 2 H,

CH_2O), 3.8 (m, 1 H, CNH), 4.12 (m, 1 H, CHO), 7.0 and 7.2 (m, 10 H, arom).

(4*S*,5*S*)-4-Benzyl-3-(*tert*-butoxycarbonyl)-5-((2*R*)-2-carboxy-3-phenylpropyl)-2,2-dimethyl-1,3-oxazolidine (14). To a suspension of PtO_2 (55 mg, 0.24 mmol) in H_2O, previously reduced with H_2 (1 atm, 1 h), was added a solution of 13 (90 mg, 0.2 mmol) in dioxane (2 mL). The mixture was warmed to 50 °C, and oxygen was bubbled through it for 36 h. Ethyl acetate (5 mL) was added, the aqueous phase was adjusted to pH 3 with 1 M HCl, and the organic layer was separated. After a second extraction with ethyl acetate (5 mL), the organic layer was washed with brine and dried on anhydrous Na_2SO_4. After evaporation of the solvent, column chromatography on silica gel (hexane/ethyl acetate, 1/4) gave product 14 (67 mg, 62% yield); mp 63–67 °C; IR (neat) ν 3100–2700, 2980, 1730, 1640 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.58 (bs, 15 H, t-Bu and Me), 1.8–2.4 (m, 5 H, 2 CH_2 or CH), 2.8 (m, 1 H, CH_2Ph) 3.0–3.4 (m, 4 H CH_2Ph and CH), 3.8 (m, 1 H, CHN), 4.05 (m, 1 H, CHO), 7.2 (m, 10 H, arom), 10.6 (bs, 1 H, OH); MS *m/e* 454 ($M^+ + 1$), 453, 381, 361, 328, 264, 220, 91, 57 (base). Anal. Calcd for $C_{27}H_{35}NO_5$: C, 71.50; H, 7.78; N, 3.09; O, 17.64. Found: C, 71.05; H, 7.69; N, 3.00.

(2*R*,4*S*,5*S*)-*N*,2-Dibenzyl-5-((*tert*-butoxycarbonyl)-amino)-4-hydroxy-6-phenylhexanamide (15). Triethylamine (0.28 g, 0.28 mmol) was added to a solution of the acid 14 (63 mg, 0.14 mmol) in CH_2Cl_2 (1 mL). BOP (62 mg, 0.14 mmol) was added, followed by benzylamine (21 mg, 0.2 mmol). After 3 h of stirring to room temperature, CH_2Cl_2 (5 mL) was added and the mixture was washed with 3 M HCl (1 mL) and 10% $NaHCO_3$ (1 mL). After the organic layer was dried over anhydrous Na_2SO_4, the solvent was evaporated and the crude product was dissolved in MeOH (2 mL). Boron trifluoride acetic acid complex (0.2 mL) was added, and the mixture stirred at room temperature for 5 h. Solid Na_2CO_3 (0.1 g) was added, and the mixture was stirred for 30 min. After filtration on Celite, the filtration cake was washed with ethyl acetate and the organic layer was dried on anhydrous Na_2SO_4. After evaporation of the solvent, column chromatography on silica gel (hexane/ethyl acetate, 1/1) gave product 15 (40 mg, 57%): mp 179–181 °C; IR (neat) ν 3350, 3260, 3010, 2980, 1700, 1645, 1540, 1480 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.41 (s, 9 H, t-Bu), 1.81 (m, 2 H, CH_2), 1.9 (bs, 1 H, OH), 2.3–2.9 (m, 4 H, CH_2Ph), 3.61 (m, 1 H, CHN), 3.75 (m, 1 H, CHN), 4.15 (m, 1 H, CHO), 4.4 (m, 2 H, CH_2N), 4.96 (bm, 1 H, NH), 5.91 (bm, 1 H, NH), 7.0–7.4 (bm, 15 H, arom); MS *m/e* 502 (M^+), 488, 91 (base); HRMS calcd for $C_{31}H_{38}N_2O_4$ 502.6539, found 502.6557.

Acknowledgment. The work was financially supported by MURST (Rome), Fondi 60%. We thank M. Botta (University of Siena) for HRMS analyses and S. Chimichi (University of Florence) for helpful suggestions in determining the absolute configuration of alcohol 3.

Supplementary Material Available: ^1H and ^{13}C NMR spectra of 4 and 5 (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of 7-Methyl-3-propyl-2(*E*),6(*E*)-nonadienyl Acetate, a Terpenoid Compound in the Male Square-Necked Grain Beetle *Cathartus quadricollis* (Guér.)

Dharmpal S. Dodd, Harold D. Pierce, Jr., and Allan C. Oehlschlager*

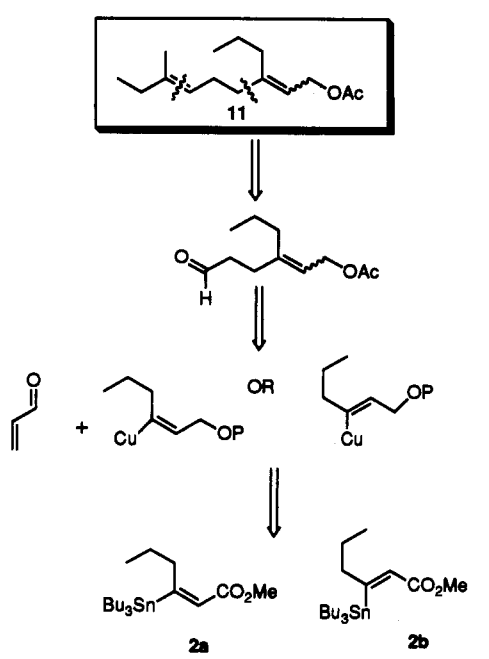
Department of Chemistry/Biochemistry, Simon Fraser University, Burnaby, British Columbia, Canada V5A 1S6

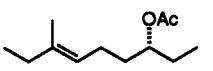
Received April 6, 1992 (Revised Manuscript Received June 12, 1992)

Introduction

In the investigation of the square-necked grain beetle, *Cathartus quadricollis* (Guér.), we identified (3*R*)-7-methyl-6(*E*)-nonen-3-yl acetate (quadrilure) as an aggregation pheromone produced by males.[1] The male beetles also produced another compound which was assigned the structure 7-methyl-3-propyl-2,6(*E*)-nonadienyl acetate (11) on the basis of a detailed analysis of its decoupled ^1H NMR spectra. However, the ^1H NMR spectra data did not permit an assignment of the C_2–C_3 double-bond geometry. Although this compound was apparently inactive in the laboratory bioassays, determination of its exact effects on the behavior of the beetles was difficult due to the small amount of the natural compound produced by the beetles. To establish the structure of this novel compound and to provide sufficient material for testing, we describe herein its synthesis.

Scheme I





Quadrilure

Results and Discussion

Retrosynthetic analysis of the 1,5-diene structure of 11 showed that both the 2(*E*) and the 2(*Z*) isomers could be readily synthesized by the application stannylcuprate chemistry currently under investigation in this and other laboratories.[2-5] As outlined in Scheme I, the appropri-

(1) Pierce, H. D., Jr.; Pierce, A. M.; Johnston, B. D.; Oehlschlager, A. C.; Borden, J. H. *J. Chem. Ecol.* **1988**, *14*, 2169.

(2) For a comprehensive list of references in the use of stannylcuprates see: (a) Hutzinger, M. W.; Singer, R. D.; Oehlschlager, A. C. *J. Am. Chem. Soc.* **1990**, *112*, 9398. (b) Singer, R. D.; Hutzinger, M. W.; Oehlschlager, A. C. *J. Org. Chem.* **1991**, *56*, 4933. (c) Sharma, S.; Oehlschlager, A. C. *J. Org. Chem.* **1991**, *56*, 770.

(3) (a) Piers, E.; Chong, J. M. *J. Chem. Soc., Chem. Commun.* **1983**, 934. (b) Piers, E.; Morton; Chong, J. M. *Can. J. Chem.* **1983**, *65*, 78. (c) Cox, S. D.; Wudl, F. *Organometallics* **1983**, *2*, 184. (d) Westmijze, H.; Ruitenberg, K.; Meijer, J.; Vermeer, P. *Tetrahedron Lett.* **1982**, *23*, 2797.

(4) (a) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron* **1989**, *45*, 363. (b) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron Lett.* **1981**, *22*, 4905. (c) Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263.

(5) (a) Oehlschlager, A. C.; Hutzinger, M. H.; Aksela, R.; Sharma, S.; Singh, S. M. *Tetrahedron Lett.* **1990**, *31*, 165. (b) Singh, S. M.; Oehlschlager, A. C. *Can. J. Chem.* **1991**, *69*, 1872. (c) See also: Lipshutz, B. H.; Ellworth, E. L.; Dimrock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065.

0022-3263/92/1957-5250$03.00/0