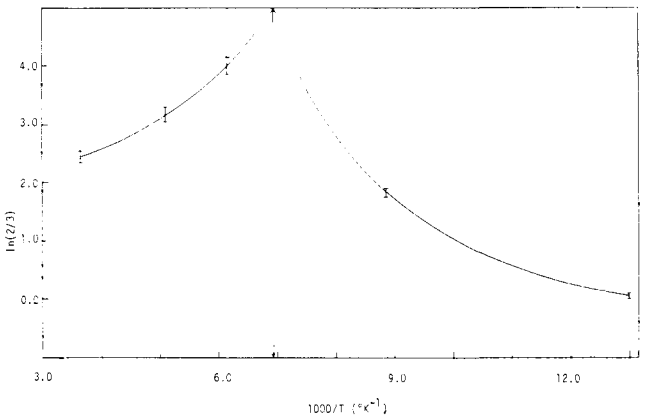

Figure 1. Product ratio as a function of temperature in reaction 1. The point marked ↑ shows melting point of the solvent.

completely suppressed in the solid-phase experiment at −196 °C, and was accompanied by a marked increase in the primary C–H insertion product. This indicates that triplet carbene chemistry is prevailing also in this matrix system and provides another example for the temperature-dependent phenomena of competitive singlet and triplet arylcarbene processes. These results, together with the spectroscopic evidence[5] that triplet arylcarbene can be generated irrespective of the organic matrices in which the low-temperature photolysis of the diazo compound is performed, apparently indicate that the key intermediate leading to the C–H insertion products in each matrix systems would be mostly triplet carbene,[6] while both singlet and triplet would participate in liquid-phase reactions.[4a,b] The decrease in the C–H insertion selectivity observed in rigid matrix is, however, completely unexpected behavior for triplet carbenes since triplet carbenes have been shown to be much more selective intermediates in the C–H insertion reaction than the corresponding singlets in gas- as well as liquid-phase experiments.[4a,b,7] The reason for the marked increase in the primary C–H insertion product in rigid matrix is then an important question.

There is a possibility that the primary C–H insertion product would be formed by combination of a benzyl radical with a primary radical (e.g., i-C_4H_9·) produced by photoisomerization of an initially formed tertiary radical (e.g., t-C_4H_9·) since such isomerization has been reported[8] to occur by UV (<300 nm) irradiation in low-temperature matrices. However, this seems unlikely since the product distributions at low temperature are essentially independent on the wavelength employed (253~366 nm). A more probable explanation is that the matrix imposes steric demand on the C–H insertion processes. Obviously the molecules which are going to participate in a matrix reaction occupy a space of a certain size and shape which depends on the relative size of guest and host molecules.[9] It is therefore not unreasonable to assume that the size and shape provided by the host molecule and its rigidity impose severe steric hindrance on the guest molecule (i.e., PhCH:) as regards the accessibility of tertiary and/or secondary C–H bonds. A similar argument can be applied to explain the dramatic change in the insertion selectivity toward the secondary C–H bonds of n-pentane with temperature. It is tempting to assume that the carbene is trapped in cages of n-pentane matrix framework in a manner in which the C–H bonds at the 3 position are brought closer to the carbene center than those at other positions. Support is lent to the above argument by examination of the results in Figure 1 which show inversion of tertiary/primary selectivity. Thus, in solution, tertiary abstraction gains over primary abstraction as temperature decreases because tertiary abstraction is favored by a lower activation energy. After the matrix is formed, continued decrease of temperature hardens the matrix and the increasing rigidity then causes primary abstraction to gain relative to tertiary abstraction.[10]

In conclusion, the present results reveal that, in addition to effects on the multiplicity of carbenes and on the mobility of molecules, a matrix imposes severe steric demands on the reactions of carbenes within it. Similar steric effect could be operative in other types of reactions of carbenes and may account for *matrix-fostered* reactions of carbene.

References and Notes

(1) (a) H. Tomioka and Y. Izawa, *J. Am. Chem. Soc.*, **99**, 6128 (1977). (b) H. Tomioka, T. Inagaki, and Y. Izawa, *J. Chem. Soc., Chem. Commun.*, 1023 (1976); *J. Chem. Soc., Perkin Trans. 1*, in press.

(2) (a) R. A. Moss and U.-H. Dolling, *J. Am. Chem. Soc.*, **93**, 954 (1971); (b) R. A. Moss and M. A. Joyce, *ibid.*, **99**, 1262 (1977); (c) R. A. Moss and J. K. Huselton, *ibid.*, **100**, 1315 (1978); (d) R. A. Moss and M. A. Joyce, *ibid.*, **100**, 4475 (1978).

(3) (a) Main product of triplet Ph_2C in liquid alcohol has been shown to be Ph_2CH_2; see, for example, D. Bethell, G. Stevens, and P. Tickle, *Chem. Commun.*, 792 (1970). (b) Moritani et al. showed that triplet $PhCCH_3$ generated in 2-butene solutions by photosensitized decomposition of the diazo compound resulted in nonstereospecific addition and no detection of C–H insertion product: Y. Yamamoto, S.-I. Murahashi, and I. Moritani, *Tetrahedron*, **31**, 2663 (1975). (c) Reference 2c shows, however, continuous behavior of the Ph_2C triplet–isobutene abstraction reaction from 0 to −196 °C.

(4) (a) W. Kirmse, "Carbene Chemistry", 2nd ed., Academic Press, New York, N.Y., 1971, p 430; (b) R. A. Moss and M. Jones, Jr., Ed., "Carbenes", Vol. I, Wiley, New York, N.Y., 1974, p 114; (c) H. Iwamura, Y. Imahashi, K. Kushida, K. Aoki, and S. Satoh, *Bull. Chem. Soc. Jpn.*, **49**, 1690 (1976); (d) G. K. Agopian, D. W. Brown, and M. Jones, Jr., *Tetrahedron Lett.*, 2931 (1976).

(5) A. M. Trozzolo, *Acc. Chem. Res.*, **1**, 329 (1968), and references cited therein.

(6) (a) Abstraction of hydrogen from C–H bonds by triplet carbene, followed by recombination, leads to apparent "insertion" products. (b) We do not completely exclude the intervention of singlet carbene in rigid matrix experiment since rapid and reversible singlet–triplet equilibrium has been assumed[4a,b] to be involved in phenylcarbene reactions. However one-step insertion of singlet carbene would become less favorable at lower temperature since the process should have a higher activation energy compared with other radical processes if one assumes triangle transition state: C. D. Gutsche, G. L. Bachman, W. Udell, and S. Bauerlein, *J. Am. Chem. Soc.*, **93**, 5172 (1971).

(7) Part of the apparent selectivity has been due to the selectivity of the abstraction reaction: R. W. Carr, Jr., *J. Phys. Chem.*, **70**, 1971 (1966); B. M. Herzog and R. W. Carr, Jr., *ibid.*, **71**, 2688 (1967); M. L. Halberstadt and J. Crump, *J. Photochem.*, **1**, 295 (1972/72); M. Jones, Jr., W. Ando, M. E. Hendrick, A. Kulczycki, Jr., P. M. Howley, K. F. Hummel, and D. S. Malament, *J. Am. Chem. Soc.*, **94**, 7469 (1972).

(8) M. Iwasaki and K. Toriyama, *J. Chem. Phys.*, **46**, 2852 (1967).

(9) (a) B. Meyer, "Low Temperature Spectroscopy", Elsevier, New York, N.Y., 1971; (b) A. M. Bass and H. P. Broida, Ed., "Formation and Trapping of Free Radicals", Academic Press, New York, N.Y., 1960.

(10) We thank a referee for drawing our attention to this point.

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Thionium Ions as Reactive Carbonyl Equivalents in Cyclization Reactions

Sir:

The high polarity and low π-bond order of the thionium group suggests that it should be more reactive toward weak nucleophiles such as aromatic rings than a simple carbonyl group. The lower activity of the latter has restricted cyclizations involving such a functional group to non-acid-labile systems. We report that thionium ions allow formation of six-membered rings with electron-rich aromatic systems.[1] Furthermore, the mildness of the conditions and the potential utility in the ergot alkaloid field is illustrated by the application to the acid-sensitive and difficultly accessible 4-substituted, 2,3-unsubstituted indole system.

Thionium ions for cyclization (eq 1) were generated in one of three ways, ionization of a thioketal, ionization of a monosulfoxide of a thioketal, or protonation of a vinyl sulfide. Since

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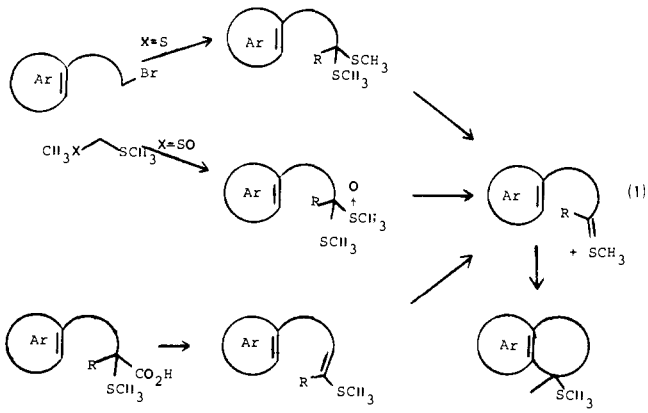
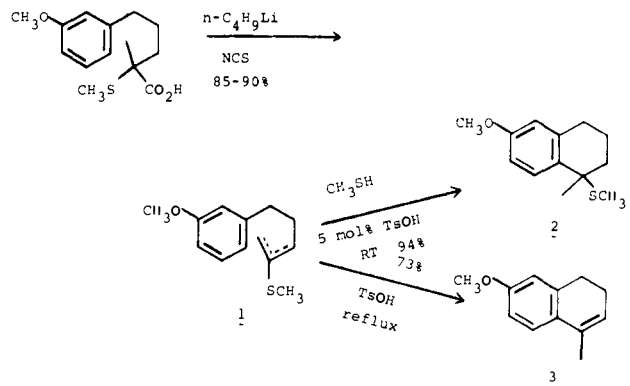
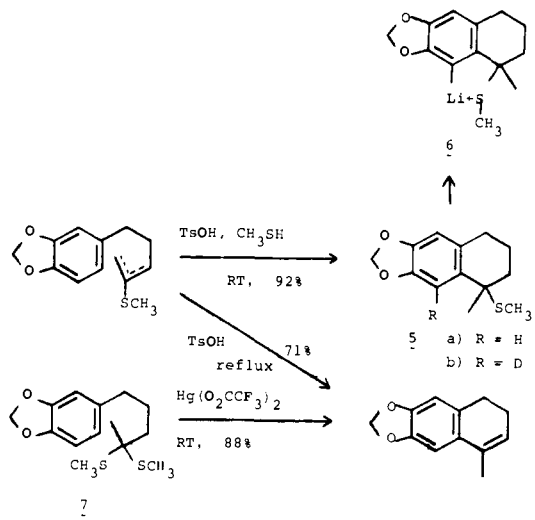


the latter is available from an α-methylthiocarboxylic acid, such a compound is also a precursor.[2] Thus, the vinyl sulfide **1**, obtained by oxidative decarboxylation of the thioacid, was treated with 5 mol % of *p*-TsOH in acetonitrile in the presence of methyl mercaptan as a buffer to give the desired cyclized product **2**[3] in nearly quantitative yield. On the other hand,

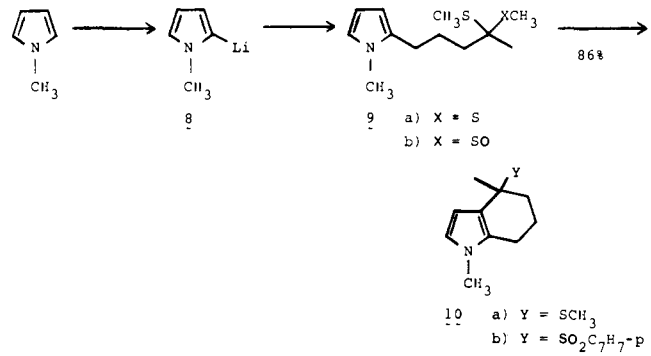


performing the reaction at reflux in the absence of a buffer led smoothly to the eliminated product **3**.[3] A similar observation was made for vinyl sulfide **4**. One advantage of the retention of the sulfur is illustrated by the directed metalation of **5a**[3] with *tert*-butyllithium which gave only **6** as determined by deuterium quenching and observing the disappearance of the peak at δ 7.0 in the NMR spectrum of monodeuterated **5b**.[4] Nearly



neutral conditions for cyclization is accessible by reacting the thioketal **7** with mercuric trifluoroacetate which leads only to cyclization and elimination to form the dihydronaphthalene.

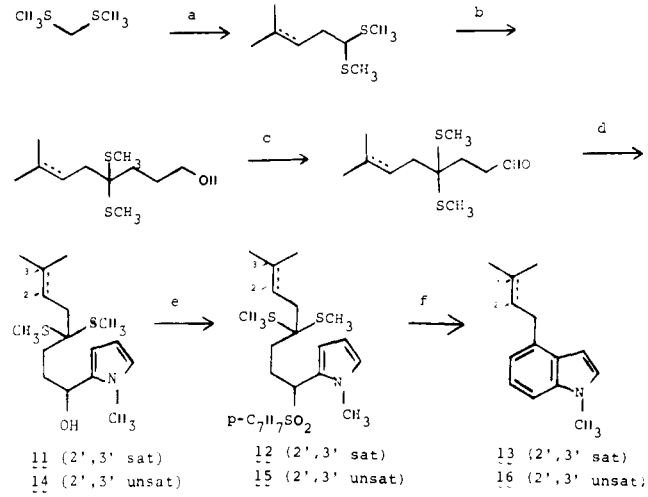
With the establishment of the reaction, we turned our attention to the acid-labile pyrrole system. The requisite substrate **9**[3] was available from the metalated pyrrole **8**[5] and 1-



chloro-4,4(dimethylthio)pentane. The sensitivity of the cyclization reaction is illustrated by observation of only decomposition products upon treatment of **9** with typical acid catalysts. On the other hand, treatment of **9b** with *p*-toluenesulfinic acid, a mild acid whose conjugate base is a good nucleophile, led smoothly to crystalline cyclized product **10b**,[3] mp 139–140 °C. In this case, the initial cyclization product **10a** undergoes exchange of methylthio for *p*-toluenesulfinyl. Attempts to aromatize **10** to the indole led only to decomposition.

A 4-substituted indole synthesis was readily accessible as outlined in Scheme I. Treatment of the unstable alcohol **11**

Scheme I. Synthesis of 4-Substituted Indoles[a]



[a] (a) C_4H_9Li, THF, $(CH_3)_2C{=}CHCH_2Br$; (b) *n*-C_4H_9Li, THF, $BrCH_2CH_2CH_2OTMS$ and then H_2O; (c) $C_5H_5NH^+ClCrO_3$, CH_2Cl_2, room temperature; (d) **8**, (e) *p*-$C_7H_7SO_2H$, CH_3CN, room temperature; (f) *p*-$C_7H_7SO_2H$, CH_3CN, 50 °C or reflux.

with 1 equiv of *p*-toluenesulfinic acid at room temperature in acetonitrile led to quantitative formation of the sulfone **12**.[3] Resubjection of **12** to *p*-toluenesulfinic acid at 50 °C in acetonitrile led to 1-methyl-4-isopentylindole (**13**)[3] in 61% yield. This rare regiocontrolled synthesis of 4-substituted indoles led us to apply this method to 1-methyl-4-(3′-methyl-2′-butenyl)indole (**16**), an intermediate toward 4-(3′-methyl-2′-butenyl)tryptophan[6] which is a biogenetic precursor of the ergot alkaloids. This example also competes a double bond with the pyrrole ring for the intermediate thionium ion. Treatment of **14** as described before, except that the second *p*-toluenesulfinic acid treatment was performed at reflux, gave the desired indole **16**[3] in 35% yield.

The use of a thionium ion as a cyclization initiator works well only with electron-rich aromatic rings as nucleophiles in which six-membered rings are formed.[7] The availability of the initial thioethers allows flexibility for further functionalization. The mildness of the conditions commends this reaction for acid-labile systems. The benzannulation approach to indole synthesis highlights this aspect. The fact that other general indole

syntheses such as the classical Fischer indole[8] and the recent Gassman indole[9] syntheses do not provide regiocontrolled entry into the 4-substituted indoles[10] (except for the case of an electron-withdrawing group such as nitro in the latter approach) which are important intermediates toward ergot alkaloids attaches special merit to this approach.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. M.R. thanks the Deutsches Forschungsgemeinschaft for partial support. M.C. thanks the Science Research Council of the United Kingdom for a postdoctoral fellowship.

References and Notes

(1) Cf. deWaard, E. R.; Rens, H. R.; Huisman, H. O. *Tetrahedron Lett.* **1973**, 4315. Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1976**, *41*, 1118.
(2) Trost, B. M.; Crimmin, M.; Butler, D. *J. Org. Chem.* **1978**, *43*, 4549. Cf. Trost, B. M.; Tamaru, Y. *J. Am. Chem. Soc.*, **1977**, *99*, 3101.
(3) **2**: NMR δ 1.54 (s, 3 H), 1.76 (s, 3 H), 1.95 (m, 4 H), 2.70 (t, J = 6 Hz, 2 H), 3.69 (s, 3 H), 6.42 (d, J = 3 Hz, 1 H), 6.61 (dd, J = 9, 3 Hz, 1 H), 7.40 (d, J = 9 Hz, 1 H). **3**: NMR δ 7.0 (d, J = 8 Hz, 1 H), 6.58 (m, 2 H), 5.62 (br t, J = 4 Hz, 1 H), 3.74 (s, 3 H), 2.68 (m, 2 H), 2.2 (m, 2 H), 1.98 (br s, 3 H). **5a**: NMR δ 1.54 (s, 3 H), 1.80 (s, 3 H), 1.70–2.10 (m, 4 H), 2.63 (m, 2 H), 5.82 (s, 2 H), 6.36 (s, 1 H), 7.0 (s, 1 H). **9**: NMR δ 1.48 (s, 3 H), 1.78 (m, 4 H), 1.97 (s, 6 H), 2.56 (m, 2 H), 3.56 (s, 3 H), 5.80 (m, 1 H), 5.90 (t, J = 3 Hz, 1 H), 6.41 (m, 1 H). **10**: NMR δ 1.60 (s, 3 H), 1.67–2.40 (m, 6 H), 2.38 (s, 3 H), 3.40 (s, 3 H), 6.03 (d, J = 3 Hz, 1 H), 6.39 (d, J = 3 Hz, 1 H), 7.09 (d, J = 8 Hz, 2 H), 7.46 (d, J = 8 Hz, 2 H). **12**: NMR δ 0.92 (d, J = 7 Hz, 6 H), 1.16–164 (m, 9 H), 1.80 (s, 3 H), 1.87 (s, 3 H), 2.40 (s, 3 H), 3.42 (s, 3 H), 4.04 (dd, J = 11, 4 Hz, 1 H), 5.72 (m, 1 H), 5.88 (t, J = 3 Hz, 1 H), 6.44 (t, J = 2 Hz, 1 H), 7.12 (d, J = 8 Hz, 2 H), 7.30 (d, J = 8 Hz, 2 H). **13**: NMR δ 0.98 (d, J = 8 Hz, 6 H), 1.64 (m, 3 H), 2.89 (br t, J = 8 Hz, 2 H), 3.80 (s, 3 H), 6.43 (d, J = 3 Hz, 1 H), 6.83 (apparent, t, J = 4 Hz, 1 H), 6.93 (d, J = 3 Hz, 1 H), 7.06 (apparent d, J = 4 Hz, 2 H). **15**: NMR δ 1.76 (s, 6 H), 3.52 (d, J = 8 Hz, 2 H), 3.76 (s, 3 H), 5.37 (t, J = 8 Hz, 1 H), 6.36 (d, J = 3 Hz, 1 H), 6.76 (apparent t, J = 4 Hz, 1 H), 6.86 (d, J = 3 Hz, 1 H), 7.00 (apparent d, J = 4 Hz, 2 H). New compounds have been fully characterized by spectral means and have satisfactory elemental composition.
(4) To our knowledge, the directive effect of a benzylic alkylthio group on aromatic ring metalation has not been previously examined. For a leading reference see Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653.
(5) Gjos, N. J.; Gronowitz, S. *Acta Chem. Scand.* **1971**, *25*, 2596.
(6) Plieninger, H.; Hobel, M.; Liede, V. *Chem. Ber.* **1963**, *96*, 1618.
(7) Attempts to use less electron-rich aromatic rings or to cyclize to form five- or seven-membered rings has led to equivocal results.
(8) Brown, R. K. *Chem. Heterocycl. Compd.* **1972**, *25*, 227.
(9) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Cue, B. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 5495.
(10) For a recent approach to 4-substituted oxindoles, see Kozikowski, A. P.; Kuniak, M. P. *J. Org. Chem.* **1978**, *43*, 2083. Renewed interest in ergot alkaloids stems in part from their possible use as prolactin inhibitors or in treatment of Parkinson's disease. See the following. Floss, H. G.; Cassady, J. M.; Robbers, J. E. *J. Pharm. Sci.* **1973**, *62*, 699. Cassady, J. M.; Li, G. S.; Spitzner, E. B.; Floss, H. G.; Clemens, J. A. *J. Med. Chem.* **1974**, *17*, 300.

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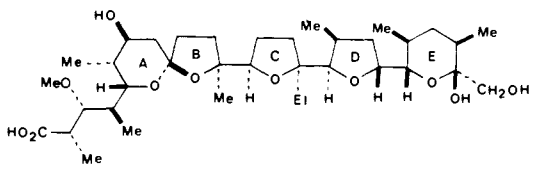
Total Synthesis of Monensin. 1. Stereocontrolled Synthesis of the Left Half of Monensin[1]

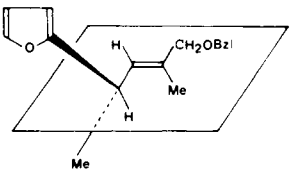
Sir:

Monensin (**1**),[2] produced by a strain of *Streptomyces cinnamonensis*, is perhaps the best known, most historical example from among a group of about 40 naturally occurring polyether antibiotics.[3] Monensin presents a formidable challenge to synthetic chemists; 17 asymmetric centers are present on the backbone of 26 carbon atoms, which means that in principle 131 072 stereoisomers exist for the antibiotic. In reporting the first total synthesis of monensin, we describe the synthesis of the left half of the antibiotic in this communication, the synthesis of the right half in the second,[4] and the total synthesis in the third.[5]



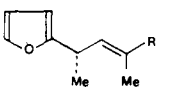
1 monensin

Wittig reaction of 2-(2-furyl)propionaldehyde[6] with carbethoxyethylidenetriphenylphosphorane in refluxing benzene afforded the trans ester **2**[7] (^{1}H NMR ($CDCl_3$) δ 1.38 (3 H, d, J = 7 Hz), 1.93 (3 H, d, J = 2 Hz), 6.70 (1 H, dq, J = 10, 2 Hz)) in 70% yield along with a small amount of the corresponding cis ester (<5% yield). Hydride reduction of **2** ($LiAlH_4$, Et_2O, RT), followed by benzylation ($C_6H_5CH_2Br$, KH, DMF–THF (1:4), 0 °C), gave the benzyl ether **3**[7] (^{1}H NMR ($CDCl_3$) δ 1.31 (3 H, d, J = 7 Hz), 1.75 (3 H, d, J = 1.5 Hz), 3.90 (2 H, br s), 4.43 (2 H, s), 5.43 (1 H, br d, J = 8 Hz)) in 95% overall yield. Hydroboration of **3** (B_2H_6, THF, 0 °C), followed by alkaline hydrogen peroxide workup, yielded the alcohol **4**[7] (^{1}H NMR ($CDCl_3$) δ 0.98 (3 H, d, J = 7 Hz), 1.29 (3 H, d, J = 7 Hz), 4.50 (2 H, s)) along with a small amount of its diastereomer in 85% yield. The ratio of **4** and its diastereomer was ~8:1. The structure assignment of **4** was made based on an example similar to this case.[8] The origin of the remarkable stereospecificity observed might be related to the conformational preference of **3**; based on the pioneering investigations by Wilson,[9] Herschbach,[10] Bothner-By,[11] and others,[12] the preferred conformation of **3** is assumed to be A. Therefore, hydroboration would take place preferentially from the sterically less hindered α face to yield **4**.

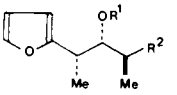


A

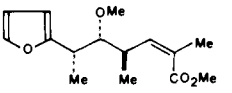
Methylation of **4** (CH_3I, KH, DMF–THF (1:4), 0 °C, followed by debenzylation (1 atm of H_2, 10% Pd/C, CH_3OH, RT), gave the alcohol **5**[7] (^{1}H NMR ($CDCl_3$) δ 0.96 (3 H, d, J = 7 Hz), 1.27 (3 H, d, J = 7 Hz), 3.21 (3 H, s)) in 88% overall yield. Optical resolution of **5** was achieved in a three-step sequence: (1) (−)-$C_6H_5CH(CH_3)N{=}C{=}O$, Et_3N at 50 °C; (2) separation of the resultant diastereomeric urethanes



2 R = $CO_2C_2H_5$
3 R = $CH_2OCH_2C_6H_5$



4 R^1 = H, R^2 = $CH_2OCH_2C_6H_5$
5 R^1 = CH_3, R^2 = CH_2OH
6 R^1 = CH_3, R^2 = CHO



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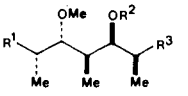

8 R^1 = 2-furyl, R^2 = H, R^3 = CH_2OH
9 R^1 = 2-furyl, R^2 = $CH_2C_6H_5$, R^3 = $CH_2OCH_2OCH_3$
10 R^1 = CO_2CH_3, R^2 = $CH_2C_6H_5$, R^3 = $CH_2OCH_2OCH_3$
11 R^1 = CO_2CH_3, R^2 = $CH_2C_6H_5$, R^3 = CH_2OH
12 R^1 = CO_2CH_3, R^2 = $CH_2C_6H_5$, R^3 = CHO

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