Deuterium substitution experiments and attempts to observe the ^{13}C hfs are planned for cubane.[21] Hopefully, deuterium substitution because of zero-point energy differences will prevent the fluxional averaging and provide information about the type of static distortion that occurs in the unusual $C_8H_8^+$ cation radical. This type of isotopic effect was observed in in $CH_4^+/CH_2D_2^+$ and allowed its ground state to be established as C_{2v}.

Acknowledgment. Project support from the National Science Foundation (CHE-8508085) is gratefully acknowledged. We (L.B.K. and C.A.A.) express our appreciation to the Camille and Henry Dreyfus Foundation for the computer equipment used to conduct the theoretical calculations.

(21) The d_1, *sym*-d_2, *sym*-d_6, and d_8 isotopic forms of cubane have previously been reported: (a) Luh, T.-Y.; Stock, L. M. *J. Am. Chem. Soc.* **1974**, *96*, 3712. (b) Della, E. W.; Patney, H. K. *Austr. J. Chem.* **1976**, *29*, 2469.

A Concise Enantioselective Synthesis of Acromelic Acid A

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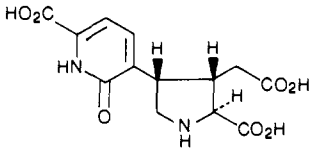
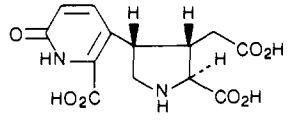
Acromelic acid A (**1**), isolated along with acromelic acid B (**2**) from the poisonous Japanese mushroom *Clitocybe acromelalga*,[1] has been revealed to exhibit the most potent depolarizing effect[2] among the kainoid amino acids ever found.[3] The structure and stereochemistry of acromelic acids A (**1**) and B (**2**) have been



acromelic acid A (1)

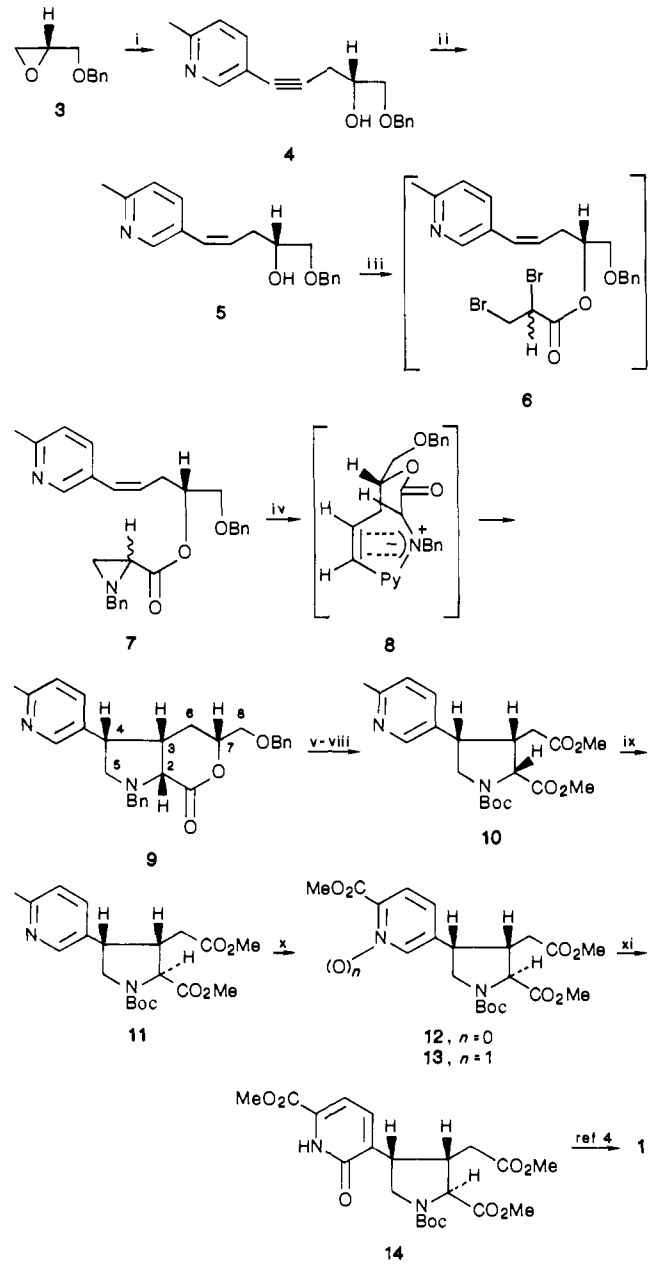


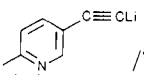
acromelic acid B (2)

established through efforts of Matsumoto and co-workers on the basis of chemical conversion of natural kainic acid into these amino acids.[4,5] This conversion implies their formal total synthesis as kainic acid has been synthesized in natural forms;[6] however, more straightforward preparation is currently required for neurochemical investigations of these interesting amino acids. We report here a concise synthesis of acromelic acid A (**1**) in natural forms starting from (*S*)-*O*-benzylglycidol (**3**) employing the intramolecular 1,3-dipolar addition[7] as the key reaction.

(*S*)-*O*-Benzylglycidol[8] (**3**) is reacted with the lithium acetylide generated in situ from 2-methyl-5-ethynylpyridine[9] to afford (76%)

Scheme I



(i)  /THF–HMPA/–70 °C-room temperature/8 h. (ii) H_2/Lindlar catalyst/benzene/quinoline (catalytic)/room temperature/24 h. (iii) $BrCH_2CHBrCOCl/Et_3N/CH_2Cl_2/0$ °C/2 h, then $C_6H_5CH_2NH_2/0$ °C/2 h. (iv) 200 °C/1.7% in *o*-$C_6H_4Cl_2$/1.5 h. (v) H_2/10%Pd–C/MeOH–HCl/room temperature/3 days. (vi) $(Boc)_2O$/3 N NaOH–dioxane (1:1)/room temperature 1 h, then aqueous $NaIO_4/0$ °C/15 min, then aqueous $KMnO_4/0$ °C/2 h. (vii) concentrated H_2SO_4 (catalyst)/MeOH/reflux/24 h. (viii) $(Boc)_2O/Et_3N/CH_2Cl_2$/room temperature/15 min. (ix) NaH (2.1 equiv)/DBU (2.5 equiv)/benzene/room temperature/5 h. (x) *m*-CPBA/CH_2Cl_2/room temperature/24 h. (xi) $(CF_3CO)_2O$(10 equiv)/DMF/room temperature/45 h.

the (*R*)-alcohol[10] **4** (Scheme I). Partial hydrogenation of **4** gives (85%) the *Z*-olefin **5**, mp 93–94 °C, $[\alpha]^{25}_D$ –10.2° (*c* 1.0, $CHCl_3$). Treatment[7] of **5** with 2,3-dibromopropionyl chloride followed by benzylamine in the same flask yields (65% overall) the aziridine **7**. Thermolysis[7] of **7** in *o*-dichlorobenzene[11] in a sealed tube affords

(1) (a) Konno, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1983**, *24*, 939. (b) Konno, K.; Hayano, K.; Saito, H.; Shirahama, H.; Matsumoto, T. *Tetrahedron* **1982**, *38*, 3281. (c) Konno, K.; Shirahama, H.; Matsumoto, T. *Phytochemistry* **1984**, *23*, 1003.

(2) Cf.: (a) McGeer, E. G.; Olney, J. W.; McGeer, P. L. *Kainic Acid as a Tool in Neurobiology*; Raven Press: New York, 1978. Watkins, J. C. *Glutamate Transmitter in the Central Nervous System*; Roberts, P. J. Storm-Mathisen, J., Johnston, G. A. R., Eds.; Wiley: Chichester, 1981; p 1.

(3) Konno, K.; Hashimoto, K.; Shirahama, H.; Matsumoto, T.; Ohfune, Y. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1985**, *27*, pp 252–258.

(4) Konno, K.; Hashimoto, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1986**, *27*, 607.

(5) Hashimoto, K.; Konno, K.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1986**, 1399.

(6) Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4978.

(7) DeShong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309.

(8) Cf.: Takano, S.; Akiyama, M.; Ogasawara, K. *Synthesis* **1985**, 503.

(9) Prepared (67% overall) from 2-methyl-5-acetylpyridine by a conventional manner: (i) PCl_5, toluene, 12 h; (ii) *t*-BuOK, *t*-BuOH, 30 min.

(10) All new isolated compounds reported herein exhibited satisfactory ^1H NMR, IR, optical rotation, and MS or combustion analytical data.

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(73%) the trisubstituted pyrrolidine **9**, $[\alpha]^{25}_D$ -72.04 °C (*c* 0.98, $CHCl_3$), as a single stereoisomer.[12] All syn stereochemistry of the product is confirmed by nuclear Overhauser effect difference spectroscopy (NOEDS) (500 MHz) of **9** which shows distinct enhancements in the 2-H, 4-H, and 7-H signals when the 3-H is irradiated.[13] Although there are four possible diastereomers which could have been produced from the azomethine ylide intermediate, it is noteworthy that only one of these with all syn stereochemistry (**9**) is produced in the cycloaddition. The extremely high diastereofacial selectivity for the cycloaddition of **7** is best in accord with the *anti*-azomethine ylide[14] **8** as the reactive conformer in which the bulky benzyloxymethyl group takes the most stable spatial arrangement to give the all syn product **9**.

Upon sequential double debenzylation, *N*-protection, glycol cleavage, esterification,[15] and *N*-reprotection, the adduct **9** yields (26% overall)[16] the dimethyl ester **10**, $[\alpha]^{24}_D$ -9.28° (*c* 0.97, $CHCl_3$). Treatment of **10** with sodium hydride in the presence of DBU allows smooth epimerization[17] (94%) to afford the trans 2/3 compound **11**, $[\alpha]^{24}_D$ +1.11° (*c* 0.72, $CHCl_3$), as a single product. Oxidation[18] of **11**, followed by esterification of the resulting acid furnishes (64%) the known triester[4,19] **12**, $[\alpha]^{28}_D$ +12.23° (*c* 0.77, $CHCl_3$) [lit.[4] +6.5° (*c* 0.73, $CHCl_3$)], with 2*S*,3*R*,4*S* configuration. Oxidation of **12** with peracid gives (72%) the *N*-oxide **13**, $[\alpha]^{22}_D$ +19.04° (*c* 1.22, $CHCl_3$), which is treated with trifluoroacetic anhydride[20] to give (64%) the pyridone[4,5,19] **14**, $[\alpha]^{26}_D$ -127.48° (*c* 1.02, $CHCl_3$) [lit.[4] -114.3° (*c* 0.74, $CHCl_3$)]. Conversion of **14** into natural acromelic acid A (**1**) has already been done in a satisfactory yield.[4]

Synthesis of acromelic acid B (**2**) from (*S*)-*O*-benzylglycidol (**3**) employing the same methodology is currently under investigation.

Acknowledgment. We thank Professor Haruhisa Shirahama, Faculty of Science, Hokkaido University, for providing spectra of synthetic intermediates.

Registry No. 1, 86630-09-3; **3**, 16495-13-9; **4**, 109552-75-2; **5**, 109552-76-3; **7**, 109552-77-4; **9**, 109552-78-5; **10**, 109552-79-6; **11**, 109552-80-9; **12**, 103314-35-8; **13**, 103314-36-9; **14**, 103335-11-1; $BrCH_2CHBrCOCl$, 18791-02-1; $PhCH_2NH_2$, 100-46-9; lithium 2-(2'-methyl-5'-pyridyl)acetylide, 109552-81-0.

(11) Xylene[7] in place of *o*-dichlorobenzene may be used; however, more vigorous conditions (sealed tube, 300 °C, 7 min) were required to obtain **9** in 68% yield.

(12) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (1 H, 6 lines, C_6-*H*(α)), 1.75 (1 H, 8 lines, C_6-*H*(β)), 2.51 (3 H, s, py_2*Me*), 2.86 (1 H, dd, *J* = 7.5 and 10 Hz, C_5-*H*(α)), 3.05 (1 H, dd, *J* = 2 and 10 Hz), C_5-*H*(β)), 3.08 (1 H, 9 lines, C_3-*H*), 3.32 (1 H, br t, *J* = 7.5 Hz, C_4-*H*), 3.39 (1 H, dd, *J* = 10 and 5 Hz, C_8-*H*), 3.48 (1 H, d, *J* = 11.25 Hz, C_2-*H*), 3.55 (1 H, dd, *J* = 10 and 6.25 Hz, C_8-*H*), 3.60 (1 H, d, *J* = 12.5 Hz, -N-benzyl-*H*), 4.38 (1 H, 10 lines, C_7-*H*), 4.48 (1 H, d, *J* = 15 Hz, -O-benzyl-*H*), 4.51 (1 H, d, *J* = 15 Hz, -O-benzyl-*H*), 4.56 (1 H, d, *J* = 12.5 Hz, -N-benzyl-*H*), 7.10 (1 H, d, *J* = 8.6 Hz, py_3-*H*), 7.15-7.5 (10 H, m, 2 × C_6H_5), 7.75 (1 H, dd, *J* = 2.8 and 8.6 Hz, py_4-*H*), 8.2 (1 H, d, *J* = 2.8 Hz, py_6-*H*). No other diastereomeric adducts are detected from the reaction mixture. Enantiomeric homogenity of the adduct **9** is ascertained by examination of the ^{1}H NMR spectra (500 MHz) of (*R*)- and (*S*)-MTPA esters derived from the primary alcohol (**9**: -OBn = -OH) which is obtained from **9** by selective *O*-debenzylation (BBr_3, -90 °C in CH_2Cl_2, 10 min).

(13) DeShong, P.; Dicken, C. M.; Staib, R. R.; Freyer, A. J.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4397.

(14) The generation of a pyrrolidine with all syn stereochemisry via an *anti*-azomethine ylide such as **8** is not unexpected in light of DeShong's results with related systems.[7]

(15) The carbamate bond is also cleft under these conditions.

(16) This sequence of reactions is carried out without purifying each intermediate.

(17) The 2,3-stereochemistry of the kainoids has shown to be readily distinguishable by ^{1}H NMR spectrum comparison.[1a] Generally, C_2-H of trans isomers resonates at higher field (ca. 0.5 ppm) than that of cis isomers; for example **10** exhibits at δ 4.05, while **11** exhibits at δ 4.50.

(18) Cf.: Jerchel, D.; Heider, J.; Wagner, H. *Justus Liebigs Ann. Chem.* **1958**, *613*, 153.

(19) The compound shows the same spectra (IR and ^{1}H NMR (500 MHz)) as those of an authentic material[4] though there is discrepancy in optical rotations.

(20) Konno, K.; Hashimoto, K.; Shirahama, H.; Matsumoto, T. *Heterocycles* **1986**, *24*, 2169.

Synthesis of 10-Selenatricyclo[3.3.3.0^{3,7}]undec-3(7)-ene. X-ray Structure of an Alkene Containing a Pyramidalized Double Bond

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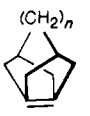
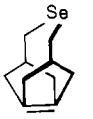
Recently we have reported the preparation of the $n = 1$[2] and $n = 2$[3] members of a homologous series of pyramidalized alkenes **1**, the spectroscopic characterization of the $n = 2$ olefin in matrix isolation,[4] and the reverse vinylcyclopropane rearrangement that these alkenes undergo on pyrolysis or on photolysis.[5] In this communication we describe the synthesis of the 10-selena derivative **2** of the $n = 3$ olefin.



1



2

A previous attempt to synthesize the $n = 3$ hydrocarbon **1** involved preparation of the diol precursor by transannular reductive ring closure[6] of bicyclo[3.3.3]undecane-3,7-dione. Unfortunately, Demjanov-Tiffeneau ring expansion of bicyclo[3.2.2]nonane-2,5-dione led, instead, to the 2,6-isomer of the desired 3,7-diketone.[7] Consequently, we turned our attention to a different route (Scheme I), involving expansion of the bridge between C-1 and C-5 in diol **3**, which had previously served as a precursor of the 9,10-benzo derivative of the $n = 2$ alkene.[8]

After protection of the diol as the acetonide, the benzene ring in **4** could be oxidatively cleaved, either with RuO_4[9] or O_3/H_2O_2,[10] to afford diacid **5**[11] in 60-80% yield. The diacid was reduced with $LiAlH_4$ to diol **6**,[11] which was converted to dimesylate **7**[11] and thence to diiodide **8**.[11] The diiodide was treated with 1 equiv of KSeCN[12] in acetone, and the crystalline monoselenacyanate **9**[11] was purified by flash chromatography and recrystallization. Ring closure was effected by slowly adding **9** to a 1:9 ethanol-THF solution of $NaBH_4$[12] under high dilution conditions, and **10**,[11] mp 120-121 °C, was isolated in 70% yield after chromatography and sublimation. The acetonide protecting group was removed by acid hydrolysis, and tricyclic diol **11**,[11] mp 267-269 °C, was converted to dimesylate **12**, which was reduced with sodium naphthalane in THF.[13] From this reaction alkene **2**[11] was isolated in 90% yield

(1) (a) University of Washington. (b) National Science Foundation Small College Faculty Summer Research Fellow. (c) Cornell University.

(2) Renzoni, G. E.; Yin, T.-K.; Borden, W. T. *J. Am. Chem. Soc.* **1986**, *108*, 7121.

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(4) Radziszewski, J. G.; Yin, T.-K.; Miyake, F.; Renzoni, G. E.; Borden, W. T.; Michl, J. *J. Am. Chem. Soc.* **1986**, *108*, 3544.

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(6) Borden, W. T.; Ravindranathan, T. *J. Org. Chem.* **1971**, *36*, 4125.

(7) Greenhouse, R.; Borden, W. T.; Ravindranathan, T.; Hirotsu, K.; Clardy, J. *J. Am. Chem. Soc.* **1977**, *99*, 6955.

(8) Greenhouse, R.; Borden, W. T.; Hirotsu, K.; Clardy, J. *J. Am. Chem. Soc.* **1977**, *99*, 1664.

(9) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(10) Berson, J. A.; Pedersen, L. D.; Carpenter, B. K. *J. Am. Chem. Soc.* **1976**, *98*, 122.

(11) This compound gave spectral and analytical data consistent with the structure assigned.

(12) Otsubo, T.; Ogura, F.; Yamaguchi, H.; Higuchi, H.; Misumi, S. *Synth. Commun.* **1980**, *10*, 595. We are indebted to Professor Reg Mitchell for calling our attention to this method.

0002-7863/87/1509-5524$01.50/0