Deuterium substitution experiments and attempts to observe the ¹³C 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 C₈H₈⁺ 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.

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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, has been revealed to exhibit the most potent depolarizing effect² among the kainoid amino acids ever found.³ The structure and stereochemistry of acromelic acids A (1) and B (2) have been



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 addition⁷ as the key reaction.

(S)-O-Benzylglycidol⁸ (3) is reacted with the lithium acetylide generated in situ from 2-methyl-5-ethynylpyridine⁹ to afford (76%)

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Scheme I



/THF-HMPA/-70 °C-room temperature/8 h. (ii) (i) H₂/Lindlar catalyst/benzene/quinoline (catalytic)/room temperature/24 h. (iii) BrCH2CHBrCOCl/Et3N/CH2Cl2/0 °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 H₂SO₄ (catalyst)/MeOH/reflux/24 h. (viii) (Boc)₂O/ Et₃N/CH₂Cl₂/room temperature/15 min. (ix) NaH (2.1 equiv)/DBU (2.5 equiv)/benzene/room temperature/5 h. (x) m-CPBA/CH₂Cl₂/ room temperature/24 h. (xi) (CF₃CO)₂O(10 equiv)/DMF/room temperature/45 h.

the (R)-alcohol¹⁰ 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, CHCl₃). Treatment⁷ of **5** with 2,3-dibromopropionyl chloride followed by benzylamine in the same flask yields (65% overall) the aziridine 7. Thermolysis⁷ of 7 in *o*-dichlorobenzene¹¹ in a sealed tube affords

⁽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.

^{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.

⁽⁹⁾ Prepared (67% overall) from 2-methyl-5-acetylpyridine by a conventional manner: (i) PCl₅, 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.

(73%) the trisubstituted pyrrolidine 9, $[\alpha]^{25}_{D}$ -72.04 °C (c 0.98, CHCl₃), 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 ylide¹⁴ 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**, $[\alpha]^{24}_{\text{D}}$ -9.28° (c 0.97, CHCl₂). Treatment of 10 with sodium hydride in the presence of DBU allows smooth epimerization¹⁷ (94%) to afford the trans 2/3 compound 11, $[\alpha]^{2\bar{4}}_{D}$ +1.11° (c 0.72, CHCl₃), as a single product. Oxidation¹⁸ of 11, followed by esterification of the resulting acid furnishes (64%) the known triester^{4,19} 12, $[\alpha]^{28}$ $+12.23^{\circ}$ (c 0.77, CHCl₃) [lit.⁴ +6.5° (c 0.73, CHCl₃)], with 2S, 3R, 4S configuration. Oxidation of 12 with peracid gives (72%) the N-oxide 13, $[\alpha]^{22}_{D}$ +19.04° (c 1.22, CHCl₃), which is treated with trifluoroacetic anhydride²⁰ to give (64%) the pyridone^{4,5,19} **14**, $[\alpha]^{26}_{D}$ -127.48° (*c* 1.02, CHCl₃) [lit.⁴ -114.3° (*c* 0.74, CHCl₃)]. 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.

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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; BrC-H₂CHBrCOCl, 18791-02-1; PhCH₂NH₂, 100-46-9; lithium 2-(2'methyl-5'-pyridyl)acetylide, 109552-81-0.

(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 dis-tinguishable by ¹H NMR spectrum comparison.^{1a} Generally, C₂-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 ¹H NMR (500 MHz)) as those of an authentic material⁴ though there is discrepancy in optical rotations.

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

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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.



A previous attempt to synthesize the n = 3 hydrocarbon 1 involved preparation of the diol precursor by transannular reductive ring closure⁶ 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 LiAlH₄ 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 KSeCN¹² in acetone, and the crystalline monoselenacyanate 9¹¹ was purified by flash chromatography and recrystallization. Ring closure was effected by slowly adding 9 to a 1:9 ethanol-THF solution of NaBH₄¹² 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

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⁽¹¹⁾ Xylene⁷ 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) &}lt;sup>1</sup>H NMR (CDCl₃, 500 MHz) δ 0.93 (1 H, 6 lines, C₆-H(α)), 1.75 (1 H, 8 lines, C₆-H(β)), 2.51 (3 H, s, py₂Me), 2.86 (1 H, dd, J = 7.5 and 10 Hz, C₅-H(α)), 3.05 (1 H, dd, J = 2 and 10 Hz), C₅-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, py₃-H), 7.15-7.5 (10 H, m, $2 \times C_6H_3$), 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 ¹H 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 (BBr₃, -90 °C in CH₂Cl₂, 10 min).
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⁽¹⁴⁾ The generation of a pyrrolidine with all syn stereochemisry via an anti-acomethine ylide such as 8 is not unexpected in light of DeShong's resultswith related systems.

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

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