In 1967, Schleyer called attention to the consequences of the torsional arrangement about $C_1C_2$ bonds in norbornyl systems and concluded that "torsional effects thus favor exo over endo attack, and, by microscopic reversibility, exo over endo departure".[6] Although Schleyer focused attention on the relief of torsional strain involving the bridgehead CH bond, the general role of the transition-state torsional interactions was clearly noted.[16]

Does *anti*-periplanar interaction (hyperconjugation) of the strained $C_1C_6$ and $C_4C_5$ bonds with the $\pi$ bond of norbornene also accelerate exo cycloaddition? An experimental test was designed as follows. Table I shows the dihedral angles for attack on bicyclo[3.2.1]oct-6-ene. The staggered arrangement of the allylic bonds in this molecule should make exo attack as rapid as that on norbornene. Tempering the staggering effect is the strain relief, which is 3.5 kcal/mol greater for norbornene than that for the [3.2.1] system. If *anti*-periplanar hyperconjugation also contributes to factor "*x*", then bicyclo[3.2.1]oct-6-ene should be much less reactive than norbornene. For example, the rate of acetolysis of *exo*-bicyclo[3.2.1]oct-6-yl tosylate is approximately the same as that of cyclohexyl tosylate,[17] which is, in turn, 477 times less reactive than *exo*-2-norbornyl tosylate.[18,19] These effects are geometrically interrelated, since the staggered arrangement of adjacent bonds automatically places one bond gauche to two vicinal bonds (minimizing closed-shell destabilization) and anti to a third (maximizing donor–acceptor stabilization), and both of these effects can contribute to torsional effects in substituted ethanes.[20] Nevertheless, a clear experimental distinction between staggering and hyperconjugation is possible in this case.

We have measured relative reactivities of bicyclo[3.2.1]oct-6-ene and norbornene toward mesitonitrile oxide[21] under competitive conditions[22] at 25 °C in $CCl_4$ solution. Norbornene is only 1.3 ± 0.2 times more reactive than bicyclo[3.2.1]oct-6-ene. Even if only 27% of the added strain relief in norbornene is felt in the cycloaddition transition state (Huisgen's most conservative estimate),[9] the activation energy of the norbornene reaction should be 1 kcal/mol lower than that for bicyclo[3.2.1]oct-6-ene. The difference is actually only 0.2 kcal/mol, so that factor "*x*" lowers the activation energy of cycloaddition to bicyclo[3.2.1]oct-6-ene by 0.8 kcal/mol more than it lowers the norbornene activation energy!

It might appear that staggering effects should allow monocyclic and acyclic systems to react as readily as norbornene in cycloadditions. However, the staggered conformations which are preferred in transition structures are different from the preferred conformations of acyclic and monocyclic alkenes. In order to achieve the preferred transition structure conformation, acyclic and monocyclic alkenes must distort in ways that introduce unfavorable interactions within the alkene moiety itself (e.g., boat for cyclohexene and a conformation with internal H–H repulsions for *cis*-3-hexene, both of which are not the preferred eclipsed lowest energy conformations). Norbornene must go through none of these gyrations. Also, such molecules are less strained and less electron rich than norbornene, and these factors contribute to reactivity with electrophilic species as well. Factor "*x*" arises from enforced staggering of allylic bonds in norbornene, not from "nonequivalent orbital extension" or hyperconjugative interactions. Indeed, there is no significant sp mixing even in highly pyramidalized alkenes, so that the staggering effects described here are the only remaining candidate for factor "x".

**Acknowledgment.** We are grateful to Professors Rolf Huisgen and Paul von Rague Schleyer for enlightening discussions, to the National Science Foundation for financial support of this research, and to the Swiss National Science Foundation for a fellowship to J.M.

**Registry No.** Norbornene, 498-66-8; bicyclo[2.2.2]oct-2-ene, 931-64-6; bicyclo[2.1.1]hex-2-ene, 822-41-3; bicyclo[3.2.1]oct-6-ene, 6491-96-9; mesitonitrile oxide, 2904-57-6; fulminic acid, 506-85-4.

(16) Our hypothesis differs in detail from that of Schleyer, who noted that the relief of torsional strain could accelerate solvolysis reactions (Schleyer, P. v. R. *J. Am. Chem. Soc.* **1964**, *86*, 1854). By contrast, we suggest that torsional interactions are as significant in transition states as they are in molecular ground states so that in attack on an $sp^2$ hybridized carbon in an alkene, carbonyl, or carbocation, staggered attack is favored over eclipsed. By microscopic reversibility, the formation of an $sp^2$ center should occur more rapidly from a staggered precursor than from an eclipsed precursor.

(17) Appleton, R. A.; Fairlie, J. C.; McCrindle, R.; Parker, W. *J. Chem. Soc. C* **1968**, 1716.

(18) Schleyer, P. v. R.; Donaldson, M. M.; Watts, W. E. *J. Am. Chem. Soc.* **1965**, *87*, 375.

(19) Hyperconjugation and bridging are undoubtedly significant in such solvolyses and in electrophilic additions to norbornenes.

(20) Brunck, T. K.;; Weinhold, F. *J. Am. Chem. Soc.* **1976**, *98*, 4392.

(21) Grundmann, C.; Richter, R. *J. Org. Chem.* **1968**, *33*, 476.

(22) Bast, K.; Christl. M.; Huisgen, R.; Mack, W. *Chem. Ber.* **1973**, *106*, 3312.

## Highly Stereoselective Approaches to α- and β-*C*-Glycopyranosides

Michael D. Lewis, Jin Kun Cha, and Yoshito Kishi*

*Department of Chemistry, Harvard University*
*Cambridge, Massachusetts 02138*
*Received May 14, 1982*

Tetrahydropyrans derived from pyranosides via substitution at C1, i.e., *C*-glycopyranosides, occur as subunits of a variety of natural products[1] and are of potential interest as chiral intermediates and enzyme inhibitors.[2] Although stereoselective routes exist for both α- and β-*C*-glycopyranosides,[3] they suffer from low yields, poor selectivity, or lack of generality. Recent requirements related to our interest in the marine natural product palytoxin[4] led us to seek a general expeditious route from simple starting materials.

It was hoped that stereochemical control could be realized by nucleophilic addition to the pyran oxonium ion derived from readily available tetrabenzylpyranose derivatives. This oxonium ion should preferentially accept nucleophiles from the α (axial) side due to the anomeric effect[5] from the ring oxygen (Figure 1).[6] By reductive process, i.e., Nu: = $H^-$, one could then obtain the opposite configuration at the anomeric center.[7] Herein is reported the successful realization of such an approach.

Thus, 2,3,4,6-tetrabenzylglucopyranose (**1**, Scheme I)[8] was reacted with allyltrimethylsilane[9] and boron trifluoride etherate in acetonitrile at ambient temperature for 3 h to yield a 10:1 mixture[10] of allylglucopyrans in 55% combined yield. Preparative thin-layer chromatographic separation allowed isolation of the α (axial) allylglucopyran **3**[11] and the β (equatorial) allylglucopyran

(1) For examples, see: McDonald, F. J.; Campbell, D. C.; Vanderah, D. J.; Schmitz, F. J.; Washecheck, D. M.; Burks, J. E.; van der Helm, D. *J. Org. Chem.* **1975**, *40*, 665. Connor, D. T.; Greenough, R. C.; von Strandtmann, M. *J. Org. Chem.* **1977**, *42*, 3664; **1978**, *43*, 5027.

(2) Shulman, M. L.; Shiyan, S. D.; Khorlin, A. Y. *Carbohydr. Res.* **1974**, *33*, 229. Cerretti, D. *Ibid.* **1981**, *94*, C10. Chmielewski, M.; BeMiller, J. N.; Cerretti, D. P. *Ibid.* **1981**, *97*, C1.

(3) Fraser-Reid, B.; Dawe, R. D.; Tulshian, D. B. *Can. J. Chem.* **1979**, *57*, 1746. Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48. Hanessian, S.; Liak, T. J.; Dixit, D. M. *Carbohydr. Res.* **1981**, *88*, C14. Pougny, J.-R.; Nassr, M. A. M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1981**, 375. Dawe, R. D.; Fraser-Reid, B. *Ibid.* **1981**, 1180 and references cited therein. See also ref 2 above.

(4) Uemura, D.; Ueda, K.; Hirata, Y.; Naoki, H.; Iwashita, T. *Tetrahedron Lett.* **1981**, 2781. Moore, R. E.; Bartolini, G. *J. Am. Chem. Soc.* **1981**, *103*, 2491.

(5) For an example: "Anomeric Effect: Origin and Consequences"; Szarek, W. A., Horton, D., Eds.; American Chemical Society: Washington, D.C., 1979; ACS Symp. Ser. No. 87.

(6) *C*-Nucleoside precursors have been made by a similar approach; however, this is not strictly orbital control solely by the ring oxygen. Ogawa, T.; Pernet, A. G.; Hanessian, S. *Tetrahedron Lett.* **1973**, 3543. Deoxygenated pyrans have also been made by a similar approach from oxonium ions derived from acetylated glycals. The additions are primarily from the axial direction, although the ratios are at best 4:1: Dawe, R. D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1981**, 1180.

(7) Recently such an oxonium ion was observed to add hydride axially through intramolecular reaction. Deslongchamps, P.; Rowan, D. D.; Rothier, N. *Can. J. Chem.* **1981**, *59*, 2787.

(8) Purchased from Sigma Chemical Co.

(9) Purchased from Petrarch Systems Inc.

(10) The ratio of stereoisomers was determined by chromatographic separation of the products.

0002-7863/82/1504-4976$01.25/0 

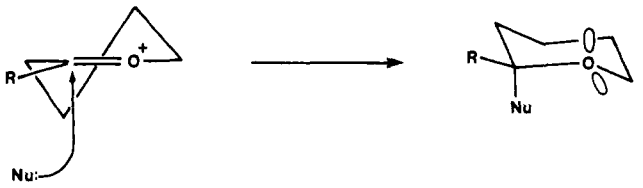
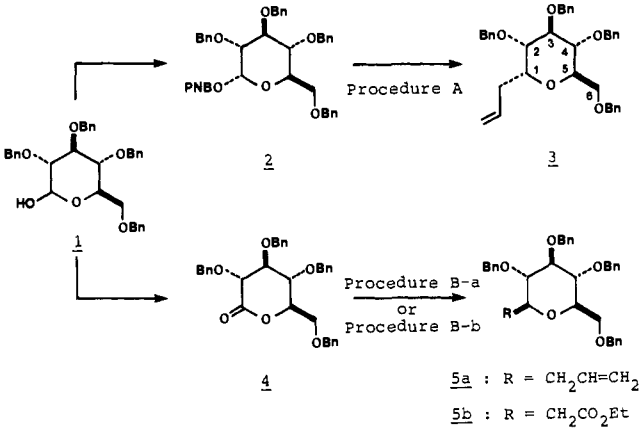


**Figure 1.**

Scheme I[a]



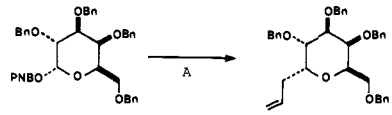
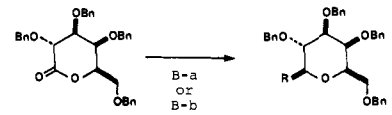
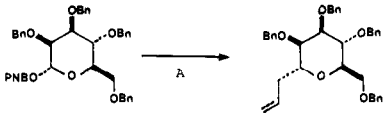
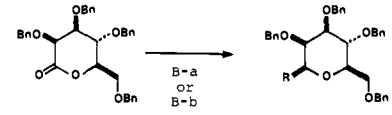
[a] Key: procedure A, $CH_2$=$CHCH_2TMS/BF_3{\cdot}Et_2O$/MeCN/0 °C → room temperature, procedure B-a, (1) $CH_2$=$CHCH_2MgBr/Et_2O$/ −78 °C, (2) $(Et)_3SiH/BF_3{\cdot}Et_2O$/MeCN/−10 °C; procedure B-b, (1) $LiCH_2CO_2Et$/THF/−78 °C, (2) $(Et)_3SiH/BF_3{\cdot}Et_2O$/MeCN/0 °C → room temperature.

**5a**.[11] Assignment of stereochemistry for **3** and **5a** was by examination of spin–spin coupling constants for the ring protons in the 270-MHz NMR spectrum of the tetraacetates derived via debenzylation ($H_2$/Pd–C/MeOH–AcOH/room temperature) and then acetylaton ($Ac_2O$/DMAP–Py/room temperature); $J_{1,2}$ = 5.8 Hz, $J_{2,3}$ = $J_{3,4}$ = $J_{4,5}$ = 9.1 Hz[12] were observed for the tetraacetate derived from **3**, while $J_{1,2}$ = $J_{2,3}$ = $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz were observed for the tetraacetate derived from **5a**. The chemical yield of the coupling reaction was greatly improved by activating the C1 position; for example, 2,3,4,6-tetrabenzyl-α-(*p*-nitrobenzoyl)glucopyranose (**2**), prepared from **1**,[13] gave a 10:1 mixture[10] of **3** and **5a** in 80% combined yield.

Conversely, treatment of 2,3,4,6-tetrabenzylglucopyranolactone (**4**)[11,14] with allylmagnesium bromide in ether gave the corresponding hemiketal, which was then reduced with triethylsilane and boron trifluoride etherate[15] in acetonitrile at −10 °C for 15 min to furnish **5a** in 85% overall yield from **4**. A similar sequence of reactions was found also practical for preparation of the glucopyranoside ester **5b**; namely, treatment of **4** with lithium ethyl acetate in THF at −78 °C[16] gave the expected aldol adduct, which was then reduced to furnish **5b**[11] in 72% overall yield from **4**. No stereoisomer was detected by either NMR or chromatographic means for this case.

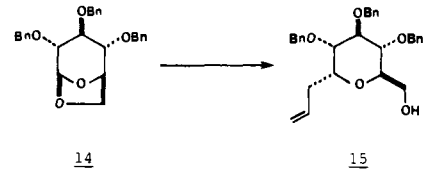
These same sequences were also performed starting from the appropriate galactose and mannose derivatives. In only one case, the reduction of the mannose series, was the stereoselectivity found

Table I

| procedure[a] | | chemical yield | stereoselectivity[b] |
|---|---|---|---|
|  | | | |
| 6[18] | 7[11,19] | 79% | 10 : 1[10] |
|  | | | |
| 8[20] | 9a[11,19] : R = $CH_2CH{=}CH_2$ | 76% | >10 : 1[10] |
| | 9b[11,21] : R = $CH_2CO_2Et$ | 79% | 1 : 0[22] |
|  | | | |
| 10[18] | 11[11,19] | 79% | >10 : 1[10] |
|  | | | |
| 12[20] | 13a[11] : R = $CH_2CH{=}CH_2$ | 67% | ca. 1 : 1[10] |
| | 13b[11,21] : R = $CH_2CO_2Et$ | 66% | 3 : 1[10] |

[a] See Scheme I. [b] The ratio of the indicated stereoisomer to its C1 epimer.

Scheme II[a]



[a] Reagents: $CH_2$=$CHCH_2TMS/BF_3{\cdot}Et_2O$/MeCN/0 °C → room temperature/20 h.

to drop significantly below a ratio of 10:1 (Table I). In these examples, presumably a manifestation of productlike steric destabilization of the transition state leading to the cis 1,2-stereochemistry is being observed.

From a practical point of view, it is important to note that these routes furnish products with easily manipulable functional groups on the newly introduced alkyl side chain. Along this line, it is worth adding that 2,3,4-tribenzyl-1,6-anhydroglucopyranose (**14**)[17] yielded the expected product **15**[11] (Scheme II) in ~60% yield under the same conditions as before. The stereoselectivity observed

(11) Satisfactory spectroscopic data (MS, NMR, IR, $\alpha_D$) were obtained for this substance. A photocopy of the $^1H$ NMR spectrum is included in the supplementary material.
(12) For the numbering in this paper, see structure **3**.
(13) Glaudemans, C. P. J.; Fletcher, H. G., Jr. *Methods Carbohydr. Chem.* **1972**, *6*, 373.
(14) Prepared by Swern oxidation [Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480] of **1**.
(15) Similar combinations of $(Et)_3SiH$ and acids are known to reduce acetals, hemiacetals, and some alcohols; for example, see: Frainnet, E.; Esclamadon, C. *C. R. Hebd. Seances Acad. Sci.* **1962**, *254*, 1814. Doyle, M. P.; DeBruyn, D. J.; Kooistra, D. A. *J. Am. Chem. Soc.* **1972**, *94*, 3659. Adlington, M. G.; Orfanopoulos, M.; Fry, J. L. *Tetrahedron Lett.* **1976**, 2955.
(16) Fieser, M.; Fieser, L. F. "Reagents for Organic Synthesis"; Wiley-Interscience: New York, 1972; Vol. 3, p 172.
(17) Prepared by benzylation ($C_6H_5CH_2Br$/NaH/THF–DMF/room temperature) of 1,6-anhydroglucose [Ward, R. B. *Methods Carbohydr. Chem.* **1963**, *2*, 394. Coleman, G. H. *Ibid.* **1963**, *2*, 397].
(18) Prepared from the corresponding tetrabenzylpyranose derivative (see ref 13).
(19) Assignment of structure for the major stereoisomer was by examination of spin–spin coupling constants for the ring protons in the high-field NMR spectrum of the tetraacetate derived via debenzylation ($H_2$/Pd–C/MeOH-AcOH/room temperature) and acetylation ($Ac_2O$/DMAP-Py/room temperature).
(20) Prepared from the corresponding tetrabenzylpyranose derivative (see ref 14).
(21) Assignment of structure for the major stereoisomer was by examination of spin–spin coupling constants for the ring protons in the high-field NMR spectrum of the pentaacetate derived via reduction (LAH/$Et_2O$/0 °C), debenzylation ($H_2$/Pd–C/MeOH–AcOH/room temperature), and acetylation ($Ac_2O$/DMAP–Py/room temperature).
(22) No stereoisomer was detected by either NMR or chromatographic means.

for **14** was ≥10:1,[10] which is very close to that observed for **1**, **2**, **6**, and **10**. Stereochemistry of **15** was established by its successful transformation into **3**.

**Acknowledgment.** The support of the National Institutes of Health (NS-12108) and the National Science Foundation (CHE-78-06296) is gratefully acknowledged.

**Registry No. 1**, 38768-81-9; **2**, 4196-36-5; **3**, 82659-52-7; **3** tetraacetate, 82659-53-8; **3** $C_1\alpha$-propyl tetraacetate, 82659-54-9; **4**, 13096-62-3; **5a**, 81972-19-2; 5a tetraacetate, 53263-18-6; **5b**, 82614-10-6; **5** (R = Pr) tetraacetate, 53263-20-0; **5** (R = $CH_2CH_2$-OAc) tetraacetate, 82598-83-2; **6**, 53081-28-0; 7, 82659-55-0; **7** $C_1\alpha$-propyl tetraacetate, 82659-56-1; **8**, 82598-84-3; **9a**, 82659-57-2; **9b**, 82598-85-4; **9b** $C_1\beta$-propyl tetraacetate, 82659-58-3; **9b** $C_1\beta$-acetoxyethyl, 82598-86-5; **10**, 61375-73-3; **11**, 82659-59-4; **11** $C_1\alpha$-propyl tetraacetate, 82659-60-7; **11** $C_1\beta$-acetoxyethyl tetraacetate, 82598-87-6; **12**, 82598-88-7; **13a**, 82659-61-8; **13b**, 82598-89-8; **13b** $C_1\alpha$ isomer, 82598-90-1; **14**, 10548-46-6; **15**, 82614-11-7; allyltrimethylsilane, 762-72-1; allyl bromide, 106-95-6; lithium ethyl acetate, 26954-26-7; 4,5,6,8-tetrabenzyl-D-gluco-2-deoxyoctan-3-ulosealdonic acid ethyl ester, 82598-91-2; 4,5,6,8-tetrabenzyl-D-galacto-2-deoxyoctan-3-ulose aldonic acid ethyl ester, 82598-92-3; 4,5,6,8-tetrabenzyl-D-manno-2-deoxyoctan-3-ulose aldonic acid ethyl ester, 82614-12-8.

**Supplementary Material Available:** Spectroscopic data for new compounds described in this paper (29 pages). Ordering information is given on any masthead page.

## Enantioselective Synthesis and Absolute Configuration of (−)-α-Kainic Acid

Wolfgang Oppolzer* and Klaus Thirring

*Département de Chimie Organique, Université de Genève CH-1211 Genève 4, Switzerland*

*Received May 21, 1982*

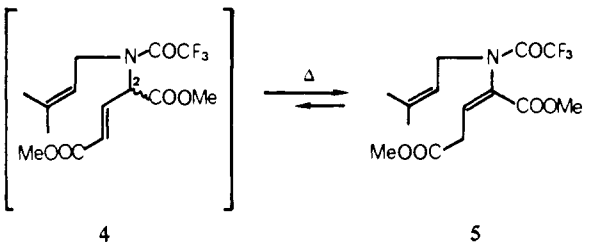
α-Kainic acid, isolated from the algae *Digenea simplex*[1] and *Centrocerus clavulatum*,[2] has been shown to possess constitution and relative configuration **1** (Scheme I) on the basis of chemical[3] and X-ray evidence.[4] Correlation of **1** with the structurally related seaweed constituents α-allokainic acid[5] (**2**) and domoic acid (**3**)[6] indicated the identity of their C(2) configuration. However, the assignment of the depicted (2*S*) configuration by means of Lutz's rule[7] may be regarded as merely tentative.[8,21] In view of the potent neuronal excitatory activity of kainic acid (**1**) and of domoic acid (**3**),[9] we aimed at an enantioselective synthesis of **1** which furthermore establishes unambiguously its absolute configuration. To this end natural (*S*)-glutamic acid appeared to be a convenient starting material; the chiral center C(2) therefrom was expected to control sterically the formation of the C(3)–C(4) bond via an

Scheme I

1, R = H
3, R = CH=CH−CH($CH_3$)COOH

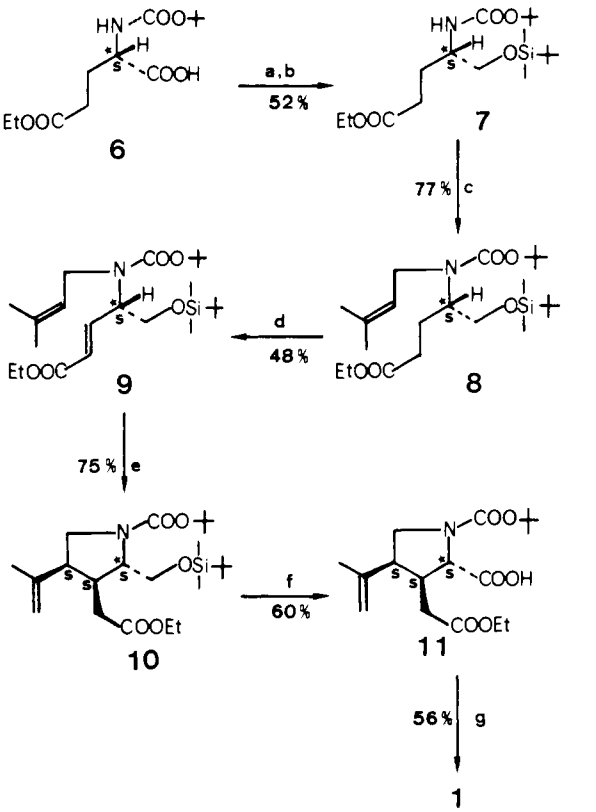
2

Scheme II



4 5

Scheme III[a]



[a] Key: (a) $BH_3$ (3 equiv), THF, −15 °C, 13 h, 57%; (b) *t*-Bu(Me)$_2$SiCl (1.2 equiv), $NEt_3$ (1.2 equiv), 4-(dimethylamino)-pyridine (0.05 equiv), $CH_2Cl_2$, room temperature, 3d, 92%; (c) NaH (1.4 equiv) was slowly added to a solution of 7 and 1-bromo-3-methyl-2-butene (1.3 equiv) in HMPA, 0 °C, 1 h at 0 °C then 16 h at room temperature, 77%; (d) (i) lithium 2,2,6,6-tetramethylpiperidide (2 equiv), THF, −78 °C, 45 min, (ii) $C_6H_5SeCl$ (1 equiv) −78 °C room temperature, (iii) 30% aq $H_2O_2$, Py, $CH_2Cl_2$, room temperature, 15 min, 48%; (e) 5% solution of 9 in toluene, 130 °C, 40 h, 70%; (f) (i) tetrabutylammonium fluoride (3 equiv), THF, room temperature, 1 h, (ii) Jones' reagent, acetone, 0 °C, 20 min, 60%; (g) (i) LiOH (10 equiv), 3:1 MeOH/$H_2O$, room temperature, 40 h, (ii) pH 2, evaporation, (iii) 1:1 $CF_3COOH/CHCl_3$, 0 °C, 1 h, (iv) treatment with ion-exchange resins[11] (56%).

(1) Murakami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026.
(2) Impellizzeri, G.; Mangiafico, S.; Oriente, G.; Piatelli, M.; Sciuto, S.; Fattorusso, E.; Magno, S.; Santacroce, C.; Sica, D. *Phytochemistry* **1975**, *14*, 1549.
(3) (a) Ueno, Y.; Nawa, H.; Ueyanagi, J.; Morimoto, H.; Nakamori, R.; Matsuoka, T. *J. Pharm. Soc. Jpn.* **1955**, *75*, 807, 811, 814. (b) Murakami, S.; Takemoto, T.; Tei, Z.; Daigo, K. *Ibid.* **1955**, *75*, 866, 869. (c) Morimoto, H.; *Ibid.* **1955**, *75*, 901, 943.
(4) Watase, H.; Tomiie, Y.; Nitta, I. *Bull. Chem. Soc. Jpn.* **1958**, *31*, 714; *Nature (London)* **1958**, *181*, 761.
(5) Nakamori, R. *Proc. Jpn. Acad.* **1956**, *32*, 35; *J. Pharm. Soc. Jpn.* **1956**, *76*, 279.
(6) Takemoto, T.; Daigo, K.; Kondo, Y.; Kondo, K. *J. Pharm. Soc. Jpn.* **1966**, *86*, 874.
(7) Lutz, O. *Chem. Ber.* **1929**, *62*, 1916. Lutz, O.; Jirgensons, Br. *Ibid.* **1930**, *63*, 448; **1931**, *64*, 1221.
(8) The $[\alpha]_D$/pH relationship of aqueous solutions of **1** and **2** was compared with those of configurationally established amino acids. Morimoto, H. *J. Pharm. Soc. Jpn.* **1955**, *75*, 941. Morimoto, H.; Nakamori, R. *Ibid.* **1956**, *76*, 26. Nakamori, R. *Ibid.* **1956**, *76*, 291. Morimoto, H. *Proc. Jpn. Acad.* **1955**, *31*, 372. See also ref 5.
(9) Shinozaki, H.; Konishi, S. *Brain Res.* **1970**, *24*, 368. Johnston, G. A. R.; Curtis, D. R.; Davies, J.; McCulloch, R. M. *Nature (London)* **1974**, *248*, 804. Biscoe, T. J.; Evans, R. H.; Headley, P. M.; Martins, M. R.; Watkins, J. C. *Brit. J. Pharm.* **1976**, *58*, 373. McGeer, E. G.; McGeer, P. L.; Singh, K. *Brain Res.* **1978**, *139*, 381. For reviews see: 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.

0002-7863/82/1504-4978$01.25/0 