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

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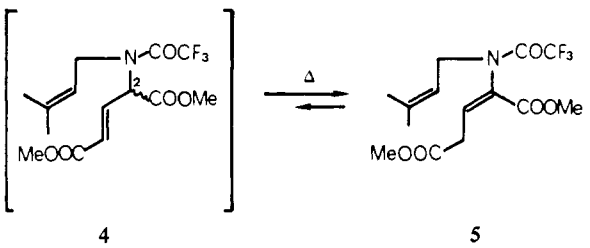
α-Kainic acid, isolated from the algae *Digenea simplex*[1] and *Centrocerus clavulatum*,[2] has been shown to possess constitution and relative configuration **1** (Scheme I) on the basis of chemical[3] and X-ray evidence.[4] Correlation of **1** with the structurally related seaweed constituents α-allokainic 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

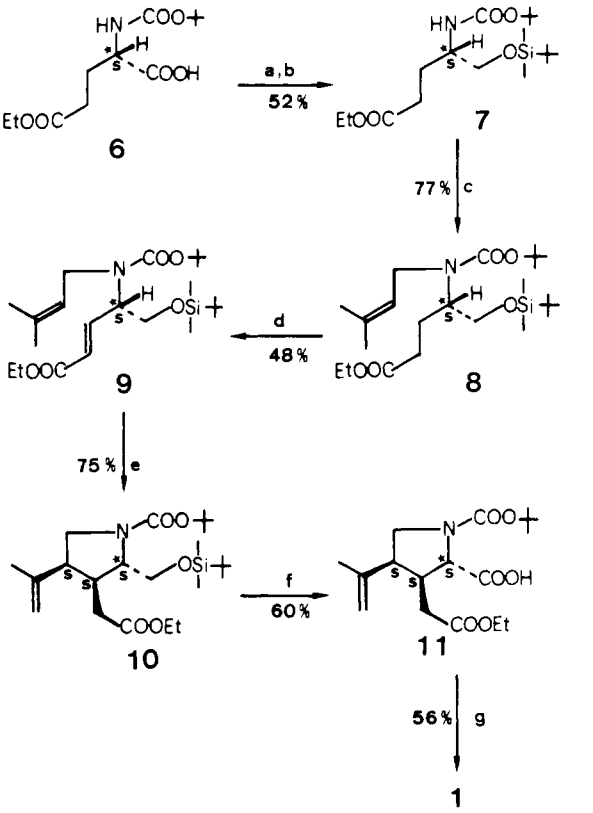
2

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%).

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

intramolecular thermal type I ene reaction[10] of an appropriate 1,6-diene intermediate.[11,12]

To avoid loss of the stereochemical integrity by a thermal olefin migration analogous to the previously observed process **4** → **5** (Scheme II, we envisaged a suitable "protection" of the α-carboxyl group by a reduction-oxidation sequence. As a corresponding control experiment *N*-benzoylprolinol was oxidized with Jones' reagent to give *N*-benzoylproline with virtually quantitative retention of configuration. Accordingly, the carboxyl group of the carbamate **6** (Scheme III),[13] prepared from commercially available (+)-5-ethyl glutamate,[14] was reduced selectively with diborane (57% yield); subsequent silylation[15] of the resulting primary alcohol furnished the *tert*-butyldimethylsilyl ether **7**[13] (92% yield). N-Alkylation of **7** with 1-bromo-3-methyl-2-butene/NaH in HMPA[11] the monoolefin **8** (77% yield). Conversion of the saturated ester **8** to the conjugated enoate **9** caused initial difficulties since all attempts to selenate **8** employing 1 equiv of various strong bases failed completely. By contrast, deprotonation of the ester **8** using 2 equiv of lithium 2,2,6,6-tetramethylpiperidide, successive selenation of the enolate, oxidation, and selenoxide elimination[16] produced smoothly the α,β-unsaturated ester **9**[13] (48% yield). The stage was now set for the crucial closure of the five-membered ring.

Heating a 5% solution of the 1,6-diene **9** in toluene at 130 °C for 40 h using a sealed Pyrex tube gave the desired pyrrolidine **10**[13] in 75% yield. As we had anticipated, the configurations of the newly formed centers C(3) and C(4) in **10** were nicely controlled in the ene process.[17] The depicted stereochemistry agrees with the ^{1}H NMR spectrum of **10**, which exhibits two singlets at δ 4.92 and 4.71, indicating the cis relationship of the isopropenyl and ethyl acetate substituents.[18] Ultimate proof of this assignment was obtained by the conversion of the ene product **10** to (−)-α-kainic acid (**1**) as described below.

Cleavage of the silyl ether moiety of **10** by treatment with tetrabutylammonium fluoride[19] and subsequent oxidation of the resulting primary alcohol with Jones' reagent furnished the carboxylic acid **11**[13] (60% yield). Saponification of **11** with LiOH, followed by removal of the *tert*-butoxycarbonyl group with trifluoroacetic acid and subsequent treatment of an aqueous solution of the evaporated reaction mixture with in-exchange resins[11] furnished enantiomerically pure (−)-α-kainic acid (56% yield), which was then recrystallized (H_2O). ^{1}H NMR analysis of the remaining mother liquor[11] showed not even a trace of other stereoisomers, thus confirming the high stereoselectivity of the key step **9** → **10**. The synthetic (−)-α-kainic acid (mp 237–243 °C dec, $[\alpha]^{20}_D$ −15.0° (*c* 0.5, H_2O) was shown to be identical with natural **1** by mixed melting point, IR, chiroptic, and ^{1}H NMR (360 MHz) evidence. Further proof for enantiomeric purity and the identity of synthetic and natural **1** was provided by ^{1}H NMR comparison of the corresponding dimethyl ester[19] in the presence of the chiral shift reagent tris(3-(trifluoroacetyl)-*d*-camphorato)europium(III).[12]

In summary, this direct approach affords (−)-α-kainic acid from (*S*)-(+)-5-ethyl glutamate in 5% overall yield and establishes the absolute configuration of the natural products α-kainic acid (**1**), α-allokainic acid (**2**), and domoic acid (**3**). It furthermore illustrates the potential to achieve steric control in intramolecular ene reactions. Finally, it seems worthwhile to advance the hypothesis that in the biosynthesis of **1**–**3** (*S*)-glutamic acid and an isoprenoid unit are joined by analogous reaction schemes involving an intramolecular ene-type reaction.

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Registry No. 1 (R = H), 487-79-6; **6**, 82598-78-5; **7**, 82598-79-6; **8**, 82598-80-9; **9**, 82598-81-0; **10**, 82614-09-3; **11**, 82598-82-1; (+)-5-ethyl glutamate, 1119-33-1.

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(11) A former synthesis of racemic α-kainic acid, based on the ~70% stereoselective, thermal cyclization of the 1,5-diene **5** (Scheme II) was postulated to proceed via the transient 1,6-diene **4**: Oppolzer, W.; Andres, H. *Helv. Chim. Acta* **1979**, *62*, 2282.

(12) For a Lewis acid mediated, enantioselective ene-type cyclization leading to a synthesis of (+)-α-allokainic acid see: Oppolzer, W.; Robbiani, C.; Bättig, K. *Helv. Chim. Acta* **1980**, *63*, 2015.

(13) IR, ^{1}H NMR (360 MHz), and mass spectra are in full agreement with the assigned structure. The following compounds showed the indicated optical rotations $[\alpha]^{20}_D$ (in CH_2Cl_2): **6**, −4.2° (*c* 0.8); **7**, −22.7 (*c* 0.88); **8**, −12.0° (*c* 1.0); **9**; −3.8 (*c* 1.0); **10**, −31.8° (*c* 0.6); **11**, −63.5° (*c* 0.25).

(14) (+)-5-Ethyl glutamate (Fluka) was treated with di-*tert*-butyl dicarbonate (1.1 equiv) and NEt_3 (1.4 equiv) in DMF/H_2O (3:2), for 4 h at room temperature following the procedure described by Moroder et al. (Moroder, L.; Hallett, A.; Wünsch, E.; Keller, O.; Wersin, G. *HoppeSeyler's Z. Physiol. Chem.* **1976**, *357*, 1651) to give **6**[13] in 99% yield.

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(17) GC/MS analysis (capillary column, quartz, 25 m, OV 101, 200 °C) of crude as well as of chromatographed **10** indicated the presence of three isomers in a ratio of 8:83:9 (retention times 48, 49, 51 min). However, the crude primary alcohol, obtained by complete (^{1}H NMR) silyl ether cleavage of **10** (80% yield), was shown to be isomerically pure by ^{1}H NMR (100 MHz, +65 °C) as well as by resilylation, which furnished GC analytically pure **10** (60% yield). Furthermore, the subsequent conversion to (−)-kainic acid was carried out with avoidance of a possible loss of stereoisomers. It thus follows that the crucial ene reaction **9** → **10** is *at least* 83% stereoselective leading to pure (−)-kainic acid without the need to separate isomers.

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(20) Following the procedure described in ref 3a, α-kainic acid was treated with saturated anhydrous HCl/MeOH at room temperature for 1 h to give the α-kainic acid dimethyl ester in 55% yield.

(21) **Note Added in Proof**: After completion and submission of this paper an enantioselective synthesis of (−)-domoic acid from L-glutamic acid via a Diels–Alder reaction has been described: Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511.

19,19,19-Trifluororetinal and 20,20,20-Trifluororetinal[1]

Alfred E. Asato, Dennis Mead, Marlene Denny, T. T. Bopp, and R. S. H. Liu*

Department of Chemistry, University of Hawaii Honolulu, Hawaii 96822

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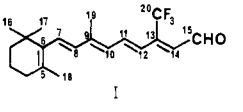
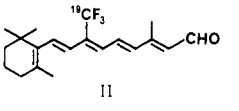
The preparation of 20,20,20-trifluororetinal (13-(trifluoromethyl)retinal), I, was reported in a recent study of the corresponding bacteriorhodopsin analogue.[2] We now disclose our results on the system and the related 19,19,19-trifluororetinal (II) as part of a study of fluorine-labeled visual pigments.[3] Since our work is not in agreement with the stereochemical assignment made for the reported all-*trans*-I, this communication emphasizes



I



II

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