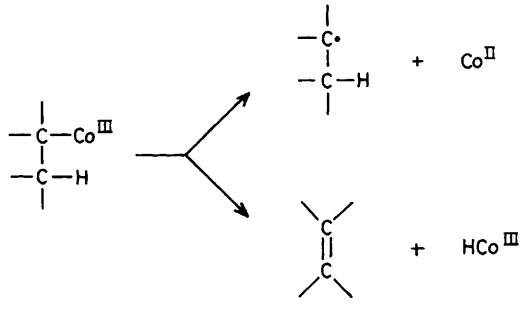
Cobalt-mediated Cyclization of Amino Acid Derivatives. Application to the Kainoids

Jack E. Baldwin* and Chun-Sing Li

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, U.K.

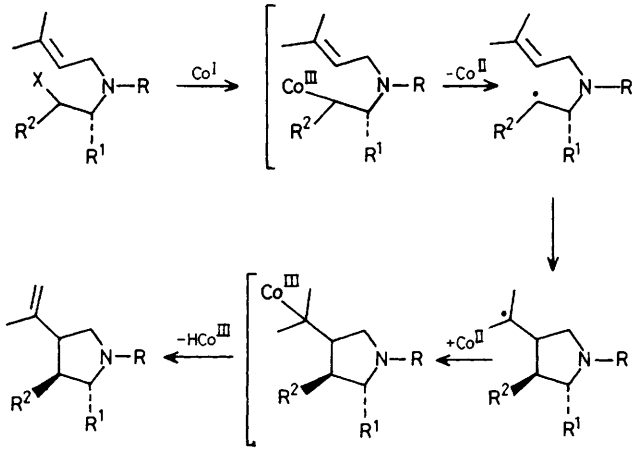
An enantiospecific route to the kainoids has been developed based on cobalt-mediated cyclization of *N*-alken-2-yl amino acid derivatives.

It is well established that alkyl–cobalt(III) species can undergo homolysis (thermal or photochemical) as well as β-eliminations[1] (Scheme 1). We now report the application of the homolysis and β-elimination sequence to the enantiospecific synthesis of substituted pyrrolidine structures found in the kainoid group of natural products (Scheme 2).[2,3] In an exploratory study L-serine ethyl ester was readily converted (30% overall) into the bromoester (**1**)† which on reaction with cobaloxime(I)[4] gave the products (**2**)—(**5**) (Scheme 3).‡ The three cyclization products were separated by h.p.l.c. and the stereochemistry of (**4a**) and (**5a**) assigned by nuclear Overhauser enhancement (n.O.e.) experiments.[5] Deprotection (NaOH hydrolysis, followed by Me_3SiI, isoprene) gave the substituted prolines (**4b**), $[\alpha]_D^{25}$ −30.5° (*c* 0.4, H_2O), and (**5b**), $[\alpha]_D^{25}$ −16° (*c* 0.23, H_2O) respectively.



Scheme 1

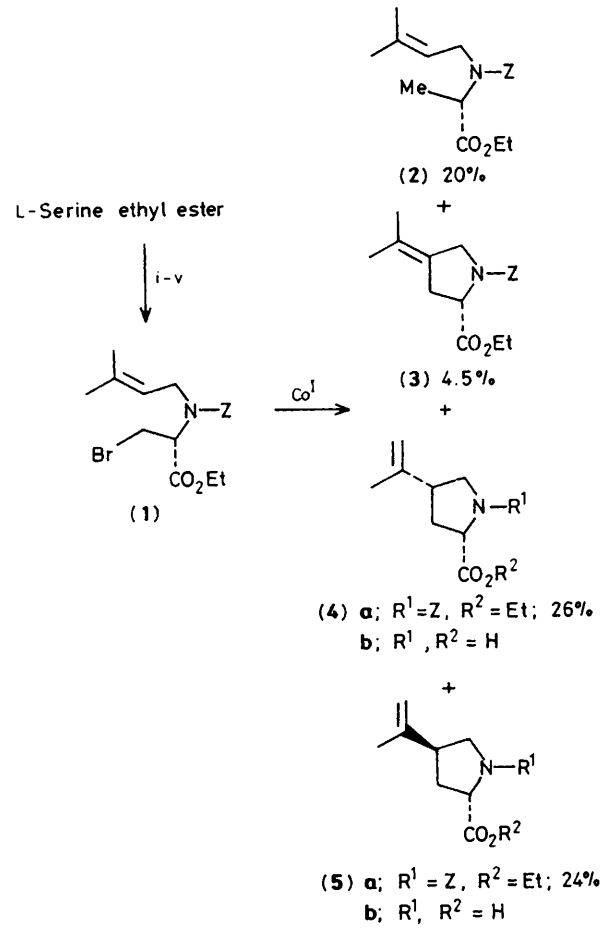
In order to assess the steric influence of substitution at the halide-bearing carbon atom, as would be expected during a synthesis of kainic acid, we repeated the reaction of Scheme 3 using L-threonine. However, problems of elimination were encountered during the conversion of the hydroxyl group into the iodide, consequently the ester function was reduced to the alcohol. The sequence then proceeded as in Scheme 4. The key iodide (**6**), obtained in 54% yield from L-threonine methyl ester was cyclised with cobaloxime(I). The two stereoisomeric proline derivatives (**7a**) and (**8a**) were desilylated and separated (flash chromatography) and then converted into the amino acids (**9**), $[\alpha]_D^{25}$ −66° (*c* 0.54, H_2O), and (**10**) $[\alpha]_D^{25}$ −22° (*c* 0.56, H_2O) in 30% overall yield for each isomer. The configuration of (**7a**) and (**8a**) were determined by n.O.e.s on



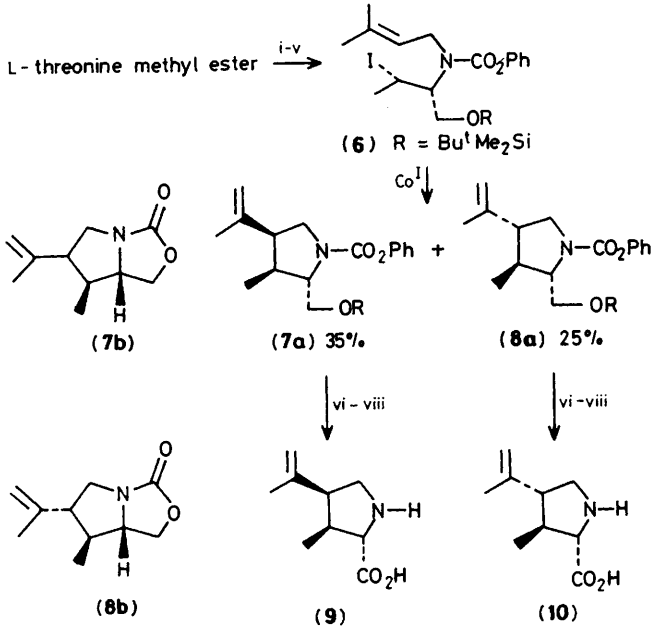
Scheme 2

† All new compounds have been characterised by spectral, mass spectral/analytical methods.

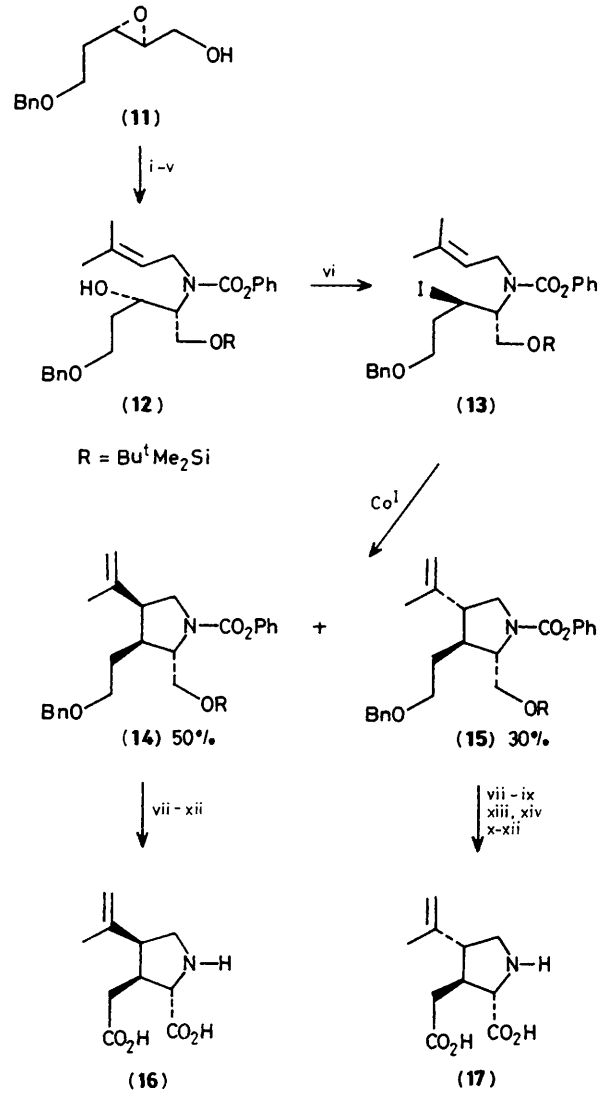
‡ Typical experimental procedure: to a suspension of chlorocobaloxime(III)[4] (1 mmol) in 40 ml of degassed methanol under a N_2 atmosphere at ice-bath temperature was added 550 μl of 10 M NaOH (5.5 mmol) and sodium borohydride (10 mmol). The mixture was stirred until a dark green solution resulted. Corresponding halide (5 mmol) in methanol was then added dropwise over a period of *ca.* 10 min. After the reaction was completed (t.l.c.) acetic acid (300 μl) was added to decompose the excess of hydride and the solvent was evaporated. The residue was diluted with water, extracted with diethyl ether, and then purified by chromatography on silica gel.



Scheme 3. *Reagents:* i, Bu^tMe_2SiCl, 4-*N*,*N*-dimethylaminopyridine (DMAP); ii, $Me_2C{=}CHCHO$, $NaBH_4$; iii, ZCl, $NaHCO_3$; iv, *p*-$MeC_6H_4SO_2OH$, MeOH; v, *N*-bromosuccinimide, Ph_3P.



Scheme 4. *Reagents:* i, $Me_2C{=}CHCHO$, then $NaBH_4$; ii, $LiAlH_4$; iii, $ClCO_2Ph$, $NaHCO_3$; iv, Bu^tMe_2SiCl, DMAP; v, $(CF_3CO_2)_2O$, pyridine, then NaI; vi, *p*-$MeC_6H_4SO_2OH$, MeOH; vii, Jones oxidation; viii, NaOH.



Scheme 5. *Reagents:* i, $Me_2C{=}CHCH_2NCO$; ii, NaH, tetrahydrofuran; iii, NaOH; iv, $ClCO_2Ph$; v, Bu^tMe_2SiCl; vi, $(CF_3SO_2)_2O$, pyridine, NaI, vii, Na, NH_3; viii, benzyloxycarbonyl chloride; ix, *p*-$MeC_6H_4SO_2OH$, MeOH; x, Swern oxidation; xi, Ag_2O; xii, Me_3SiI, isoprene; xiii, Pt–O_2: xiv, CH_2N_2.

the derivatives (**7b**) and (**8b**) and showed conclusively that this route provides selectively the required (2*S*,3*S*) absolute stereochemistry of the kainoids, as shown in Scheme 2.[5]

The application of this method for the synthesis of (−)-α-kainic and (+)-allokainic acid was now possible in the light of these findings and proceeded as in Scheme 5. In this case the key acyclic precursor (**13**) was most readily obtained from the epoxide (**11**), itself readily accessible through the corresponding allylic alcohol by the Sharpless procedure,[6] followed by an intramolecular delivery of the amino function.[7] The cobaloxime mediated cyclization of (**13**) gave the separable isomers (**14**) and (**15**) with the (−)-α-kainic acid stereochemistry predominating (1.7:1).[5] Standard transformations, as before, of deprotection and oxidation gave separately (−)-α-kainic acid (**16**), $[\alpha]_D^{25}$ −13° (*c* 0.06, H_2O) [27% from (**14**)] and (+)-α-allokainic acid (**17**), $[\alpha]_D^{25}$ +6.2° (*c* 0.34, H_2O) [14% from (**15**)].

In summary, the sequential alkyl–cobalt(III) homolysis and β-elimination provides a new entry to optically pure kainoids, derived from suitable N-2-alkenyl amino acid derivatives.

We thank P. De Shong for a sample of α-allokainic acid.

Received, 1st October 1986; Com. 1397

References

1 R. D. W. Kemmitt and D. R. Russell in 'Comprehensive Organometallic Chemistry,' eds. G. Wilkinson, F. G. A. Stone, and E. W. Abel, Pergamon Press, Oxford, 1982, vol. 5, pp. 80—131; J. M. Pratt and P. J. Craig, *Adv. Organomet. Chem.*, 1973, **11**, 331; D. Dodd and M. D. Johnson, *J. Organomet. Chem.*, 1973, **52**, 1.

2 For recent synthesis of kainoids: kainic acid: W. Oppolzer and K. Thirring, *J. Am. Chem. Soc.*, 1982, **104**, 4978 and references therein; allokainic acid: P. De Shong and D. A. Kell, *Tetrahedron Lett.*, 1986, **27**, 3979 and references therein; domoic acid: Y. Ohfune and M. Tomita, *J. Am. Chem. Soc.*, 1982, **104**, 3511; acromelic acid A: K. Konno, K. Hashimoto, and Y. Ohfune, *Tetrahedron Lett.*, 1986, **27**, 607; acromelic acid B: K. Hashimoto, K. Konno, H. Shirahama, and T. Matsumoto, *Chem. Lett.*, 1986, 1399.

3 For other applications of organocobalt chemistry in organic synthesis: review: R. Scheffold, G. Rytz, and L. Walder in 'Modern Synthetic Methods,' ed. R. Scheffold, 1983, vol. 3, pp. 355—440; Functionalized butyrolactones: H. Bhandal, G. Pattenden, and J. J. Russell, *Tetrahedron Lett.*, 1986, **27**, 2299; (b) M. Okabe and M. Tada, *J. Org. Chem.*, 1982, **47**, 5382; M. Okabe, M. Abe, and M. Tada, *ibid.*, 1982, **47**, 1775; heterocycles: (c) V. F. Patel, G. Pattenden, and J. J. Russell, *Tetrahedron Lett.*, 1986, **27**, 2303.

4 Cobaloxime(I) was prepared *in situ*: G. N. Schrauzer, *Inorg. Synth.*, 1968, **11**, 61; or by sodium borohydride reduction of chlorocobaloxime(III): see reference 3(b).

5 For stereochemical studies of intramolecular radical cyclization reactions: K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y.-D. Wu, F. K. Brown, D. C. Spellmeyer, J. T. Metz, Y. Li, and R. J. Loncharich, *Science*, 1986, **231**, 1108; (b) A. L. J. Beckwith and C. H. Schiessen, *Tetrahedron*, 1985, **41**, 3925.

6 J. G. Hill, K. B. Sharpless, C. M. Exon, and R. Regenye, *Org. Synth.*, 1985, **63**, 66.

7 W. R. Roush and M. A. Adam, *J. Org. Chem.*, 1985, **50**, 3752 and references therein.