Bull. Soc. Chim. Belg. vol.93/n° 7/1984

Lecture given at the Xth European Colloquium on Heterocyclic Chemistry, Kaiserslautern, October 1984.

NOVEL SYNTHETIC APPROACHES TO MONOCYCLIC β-LACTAM ANTIBIOTICS

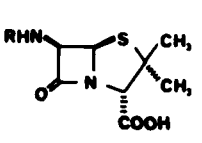
Stephen Hanessian, Soumya P. Sahoo, Claude Couture and Heinz Wyss

Department of Chemistry, Université de Montréal, C.P. 6210, Succ. A, Montréal, Québec CANADA H3C 3V1

Summary: Access to optically active 3- and 3,4-substituted azetidinones and to β-substituted amino acids is reported with applications in the area of monobactam antibiotics.

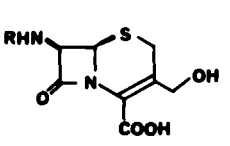
As a group of medicinally important compounds, few if any have commanded the interest of synthetic organic chemists as the β-lactam antibiotics.[1] The history of these fascinating molecules which spans close to half a century, is adorned with remarkable achievements and milestone discoveries on several frontier areas of science. Nature continues to produce novel types of highly bioactive β-lactam type antibiotics, thus challenging the laboratory scientist in many disciplines. In response, the microbiologist, the chemist and other experts in related fields have joined forces in their quest to conquer these structures, with the discovery of innovative isolation techniques and ingeneous synthetic strategies. Figure 1 illustrates the structures of several generations of naturally-occurring β-lactam antibiotics.

Figure 1



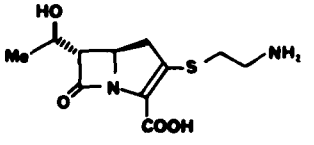
PENICILLIN

(PENAM)



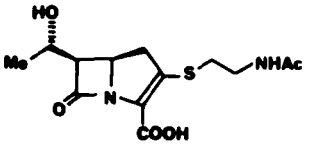
CEPHALOSPORIN

(CEPHEM)

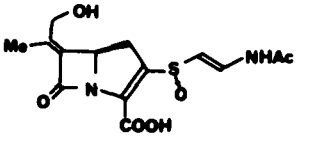


THIENAMYCIN

(CARBAPENEM)



OLIVANIC ACID

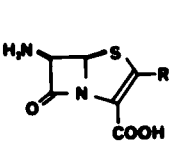


ASPARENOMYCIN

The penicillins and cephalosporins have been subjected to a relentless barrage of functional group and structural modification over the last several decades. Indeed, much novel chemistry has emerged as a result of these studies and the benefits to mankind have been enormous. With the discovery of thienamycin,[2] a member of the carbapenem group of β-lactam antibiotics, and an extremely potent antibacterial agent, an enormous potential for synthetic exploration emerged.[3,4] Great efforts have been made in chemical modification in order to obtain more stable yet equally potent analogs. On a parallel front, ingeneous synthetic schemes have been devised which have culminated in a number of elegant syntheses of thienamycin[5] and its analogs.[3,4] Structurally-related, but stereochemically different analogs have also been found in Nature as exemplified by the olivanic acids[6] and the asparenomycins.[7]

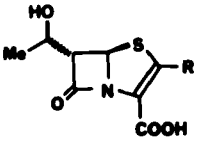
As a result of deductive reasoning, the late R.B. Woodward proposed the structures of the penems, in which the thiazolidine ring of the penicillin nucleus was replaced by a Δ-2 thiazoline moiety.[8] After a series of elegant syntheses,[9] it was found that the penems were endowed with antibacterial activity, even though the traditionally accepted N-acylamino side-chain was not present.[10]

Figure 2



PENEM

R = H, etc



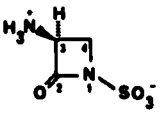
6-HYDROXYETHYL PENEM

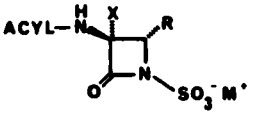
R = H, CH_2OH, SEt, etc

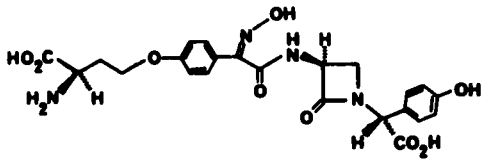
With the emergence of thienamycin, it was not surprising that the 6-α-(α-hydroxyethyl) penems and their analogs became targets for synthesis. Indeed, through the efforts of several groups,[8-15] such new-breed, hybrid β-lactam antibiotics have proved to possess remarkable antibacterial activity.

The newest entries in the arsenal of medicinally important β-lactam antibiotics are the so-called monobactams[16] (Figure 3). Their monocyclic structures baffled those who for years maintained that the somewhat strained bicyclic structure of β-lactam antibiotics was a prerequisite for antibiotic activity. Their structural simplicity, compared to other

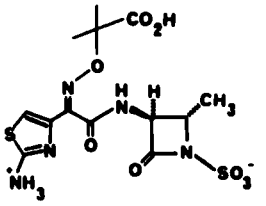
Figure 3





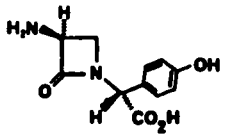


NOCARDICIN A



AZTHREONAM

(SQ 26,776)



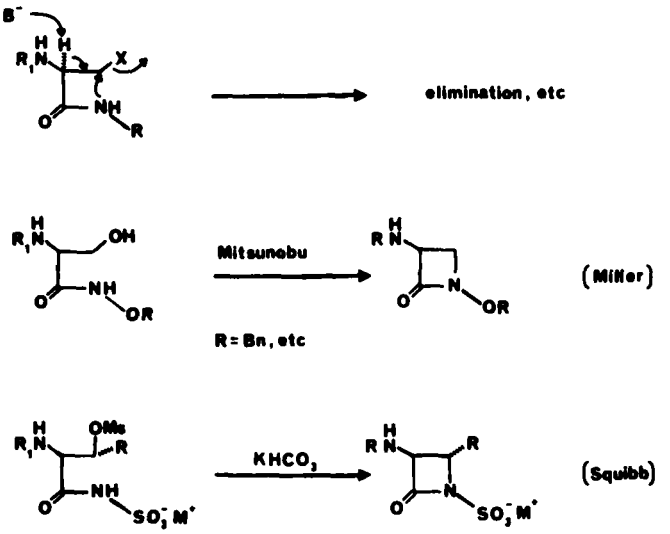
AMINO NOCARDICINIC ACID

older members of this class of compounds, led to expeditious and efficient syntheses of the 3(S)-3-aminoazetidinone ring[17] and its analogs.[18]

The nocardicins are another family of biologically active monocyclic β-lactam antibiotics.[19] Several other newer structures have emerged, including some with a cis junction at the C-3/C-4 positions.[20]

Soon after the discovery of the nocardicins, several groups reported on their studies directed toward the synthesis of this antibiotic.[21,22] Several workers have reported on synthetic approaches to the 3-amino nocardicinic acids.[23-26] Ring closure was effected by intramolecular attack of a nitrogen atom on the terminal carbon atom bearing a transient or suitably affixed leaving group. The Mitsunobu procedure,[25,27,29] the hydroxamate method[24,28] and other neutral or base-catalyzed ring closure methods[21-23] to form azetidinones have had a great deal of success. The monobactams and the 4-substituted azetidinone derivatives have also been synthesized by the same ring closure techniques, particularly via O-alkyl-hydroxamates and hydroxamate sulfonic acids.[17] This follows initial observations made with O-alkyl hydroxamic acid derivatives of β-hydroxy amino acids.[28] The NH hydrogen in these derivatives is much more acidic than in the case of amides, hence its greater nucleophilic character during the ring closure process. With other N-protecting groups, cyclization may also be accompanied by side-reactions[26] such as elimination (giving dehydroamino acids) or aziridine formation (Figure 4).

Figure 4



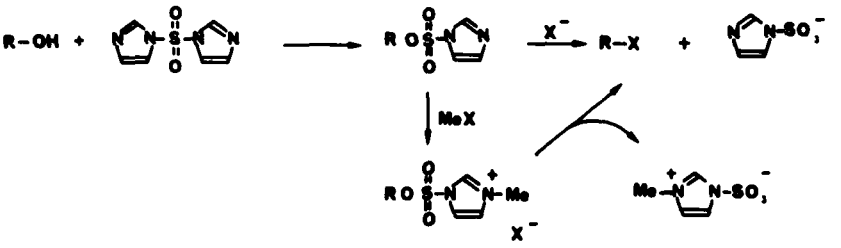
Development of a Novel Leaving Group - Applications to the Synthesis of Monobactams.

As discussed above, it is clear that azetidinone formation by intramolecular attack of an "amide"-type NH onto the terminal carbon atom of a serine derivative for example depends not only on the pKa of the NH group, but also on the nature of the leaving group on the distal carbon atom.

Traditionally less emphasis has been placed on the development of leaving groups in nucleophilic displacement reaction. In recent years, triflates have proven to be excellent leaving groups, and many applications have been reported.[29] Recently, we reported on the O-imidazolylsulfonate(imidazylate) group,[30] which by virtue of its structure and functionality, presents a different notion of reactivity as a leaving group, bringing into play, kinetic and thermodynamic parameters (Figure 5).

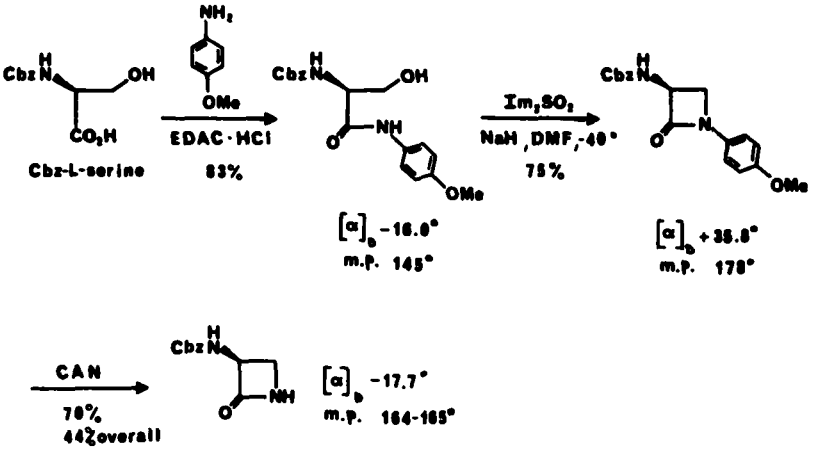
It therefore occurred to us that the imidazylate group might be an excellent leaving group for the intramolecular formation of azetidinones. In this regard it was of interest to see if an amide function could be used as an internal nucleophile without the unwanted side-reactions of elimination and/or aziridine formation.[26] As a prototype for this

Figure 5



this reaction, we chose N-Cbz-L-serine p-methoxyphenylamide (Figure 6). When treated with sulfonyl (bis-imidazole)[31] in DMF containing sodium hydride, smooth conversion into the corresponding azetidinone took place at -40°.[32] Oxidative removal[33] of the p-methoxyphenyl

Figure 6



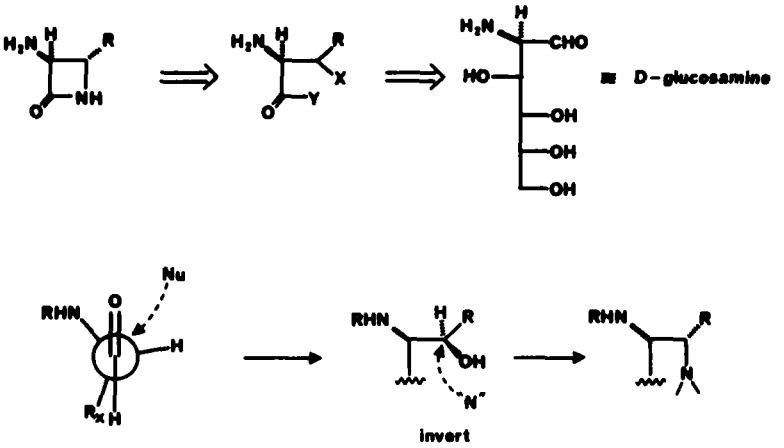
group gave the known,[34] crystalline 3(S)-3-benzyloxycarbonylamino azetidinone in good overall yield. It was therefore evident that the imidazylate group was nicely suited for this type of ring-closure in spite of the low nucleophilicity of the NH group of the amide. It is also important to note that little if any elimination was observed under the conditions of the reaction. Furthermore, no detectable epimerization had taken place at the 3-position. The same strategy has also been successfully applied for the synthesis of 3-aminonocardicinic acid in our laboratories, and other applications are undoubtedly possible in this field.

An approach to the Monobactams from Carbohydrate Precursors

In examining the stereochemical features of 4-substituted azetidinones, and in relating their functional characteristics to appropriate synthetic precursors,[35] it occurred to us that relatively easy access could be envisaged by considering open-chain, amino sugar derivatives. We have previously demonstrated the utility of carbohydrates in a formal synthesis of thienamycin.[36]

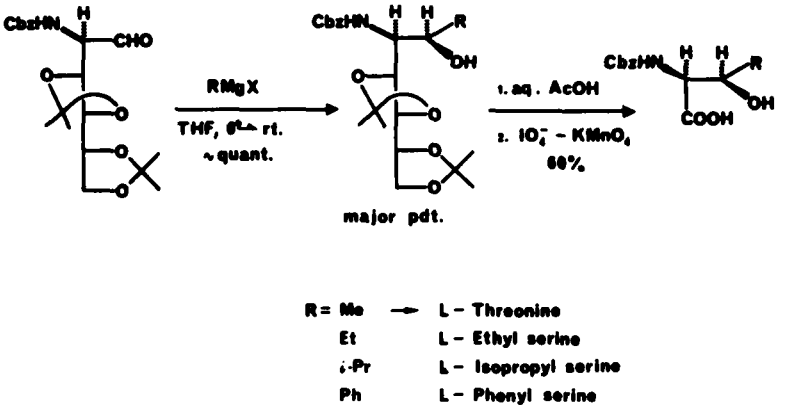
Thus, by taking azthreonam[37] as an initial target, we can see that the three carbon atoms of the β-lactam ring could converge with C-1–C-3 of 2-amino-2-deoxy-D-glucose (Figure 7). Therefore, the main challenge resided in being able to effectively chain-extend

Figure 7



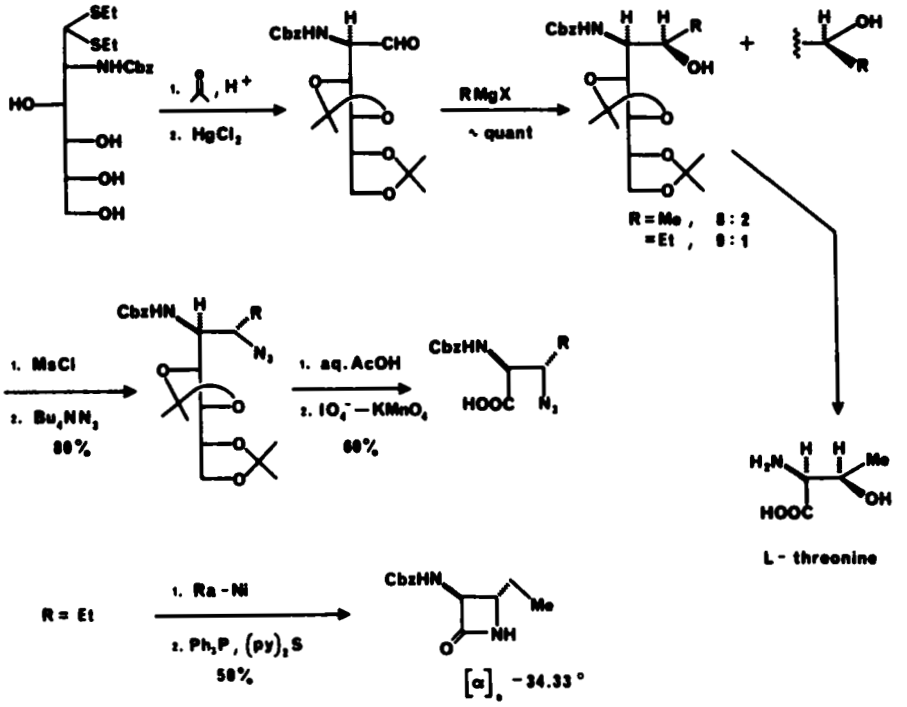
from the aldehyde end, thus introducing the C-4 substituent as well as a locus for ring closure. It was anticipated that a Grignard reaction might in fact prove to be stereoselective, particularly in view of a Cram-type approach. When the readily available aldehydo derivative of 2-benzyloxycarbonylamino-2-deoxy-D-glucose[38] was treated with various Grignard reagents, preponderant to exclusive attack took place from the anticipated face of the aldehyde carbonyl to give the corresponding β-hydroxy amino sugar derivatives (Figure 8).[39] In the case of the methyl derivative, a 4:1 ratio of isomers was obtained. The

Figure 8



major product was correlated with authentic L-threonine. With ethylmagnesium bromide, the corresponding ethyl derivative was obtained in a 9:1 ratio. The major isomer was then transformed into the corresponding optically active 3-amino-4-ethyl azetidinone derivative by a sequence involving introducton of a potential β-amino group (as azide), oxidative degradation of the polyol, and ring closure by the Ohno procedure[40] (Figure 9). It should be noted that a number of other β-lactam ring closure methods were attempted, but with limited success.[41] Also, the biologically active trans-3-(S)-N-substituted-4-(S)-ethyl-2-oxo-1-azetidine-1-sulfonic acid is described as the DL-compound.[37] Hence our approach provides access to an optically active immediate precursor.

Figure 9



Bulkier Grignard reagents gave higher stereoselection (~100:1) as is evident in the case of phenylmagnesium bromide. In this case, oxidative degradation should lead to L-phenylserine, an amino acid which is not readily available[42].

The above described strategy uses a portion of the carbohydrate framerwork, its inherent functionality and stereochemistry to control a new asymmetric center. It provides easy access to β-substituted amino acids, with excellent stereochemical outcome. There is a disadvantage in that three carbon atoms of the original carbohydrate (C-4–C-6) have to be sacrificed during the oxidative degradation process which generates the 2,3-disubstituted-2-amino acids. However, in view of the fact that the starting sugar is readily available and inexpensive, and the obvious synthetic applications, the burning-off of two asymmetric centers can perhaps be tolerated in this case.

Acknowledgments. We thank the National Scientific and Engineering Council of Canada, the Ministère de l'éducation du Québec for funding. We also acknowledge financial assistance for Sandoz Research Laboratories, Vienna, and a fellowship to H.W. from the Swiss Government. We thank Dr. Phan Viet Tan for 400 MHz spectra and Michael Evans for mass spectra.

References:

1. For a recent treatise, see "Chemistry and Biology of β-Lactam Antibiotics", R.B. Morin and M.Gorman, eds., Vol. 1-3, Academic Press, N.Y., 1982; see also Cephalosporins and Penicillins, Chemistry and Biology, E.H. Flynn, ed., Academic Press, N.Y., 1972.
2. G. Albers-Schönberg, B.H. Arison, E.A. Kaczka, F.M. Kahan, J.S. Kahan, B. Lago, W.M. Maiese, R.E. Rhodes and J.L. Smith, 16th Intersci. Conf. Antimicrob. Agents Chemother., Chicago, Ill., Paper No. 229; J.S. Kahan, F.M. Kahan, R.Guegelman, S.A. Currie, M. Jackson, E.O. Stapley, T.M. Miller, D. Hendlin, S. Mocharles, S. Hernandez and H.B. Woodruff, 16th Interscience Conf. Antimicrob. Agents Chemother., Chicago, Ill., Paper No. 227.
3. For recent review on the synthesis of carbapenem antibiotics, see, T. Kametani, Heterocycles, 17, 463-506 (1982).

4. R.W. Ratcliffe and G. Albers-Schönberg, in "Chemistry and Biology of β-Lactam Antibiotics", R.M. Morin and M. Gorman, eds., Vol. 2, Academic Press, N.Y. 1982, pp. 227-313.
5. See for example, T.N. Salzmann, R.W. Radcliffe, B.G. Christensen and F.A. Bouffard, J. Am. Chem. Soc., 102, 6161-6163 (1980).
6. A.G. Brown, D.F. Corbett, A.J. Eglington and T.T. Howarth, J. Chem. Soc., Chem. Comm., 523-525 (1977); P.J. Cassidy, G. Albers-Schönberg, R.T. Goegelman, T. Miller, B. Arison E.O. Stapley and J. Birnbaun, J. Antibiotics, 34, 637-648 (1981).
7. N. Tsuji, K. Nagashima, M. Kobayashi, J. Shoji, T. Kato, Y. Terui, N. Nakai and M. Shiro, J. Antibiotics, 35, 23-31 (1982); see also K. Okano, Y. Kyotani, H. Ishihama, S. Kobagashi and M. Ohno, J. Am. Chem. Soc., 105, 7186-7187 (1983).
8. I. Ernest, in "Chemistry and Biology of β-Lactam Antibiotics", R.B. Morin and M. Gorman, eds., Academic Press, N.Y. Vol. 2, 1982, pp. 315-360.
9. I. Ernest, J. Gostesli and R.B. Woodward, J. Am. Chem. Soc., 101, 6301-6305, (1979) and previous papers.
10. H.R. Pfaendler, J. Gosteli, R.B. Woodward and G. Ribs, J. Am. Chem. Soc., 105, 4526-4531 (1981).
11. R.B. Woodward, as cited in ref. 8, p. 347.
12. H.R. Pfandler, J. Gosteli and R.B. Woodward, J. Am. Chem. Soc., 102, 2039-2043 (1980).
13. A. SanFilippo, C. Della Bruna, D. Jabes, E. Morivillo, G. Schioppacassi, G. Fraceschi, F. Arcamone, C. Battistini, M. Foglio and F. Zarini, J. Antibiotics, 35, 1248-1250 (1982); see also, M. Foglio, C. Battistini, F. Zarini, C. Scarafile and G. Franceschi.
14. S. Oida, A. Yoshida, T. Hayashi, N. Takeda, T. Nishimura, and E. Ohki, J. Antibiotics, 33, 107-109 (1980).
15. A. Afonso, F. Hon, J. Weinstein, A.K. Ganguly and A.T. McPhail, J. Am. Chem. Soc., 104, 6138-6139 (1982).
16. R.B. Sykes, C.M. Cimarusti, D.P. Bonner, K. Bush, D.M. Floyd, N.H. Georgopapadakou, W. Koster, W.C. Liu, W.L. Parker, P.A. Principe, M. L. Rathum, W.A. Slusarchyk, W.H. Trejo and J.S. Well, Nature, 291, 489-491 (1981); see also A.I. Mada, K. Kitano, K. Kintaka, Muroi and M. Asai, Nature, 289, 590-591 (1981).
17. D.M. Floyd, A.W. Fritz and C. Cimarusti, J. Org. Chem., 47, 176-178 (1982); E.M. Gordon, M.A. Ondetti, J. Pluscec, C.M. Cimarusti, D.P. Bonner and R.B. Sykes, J. Am. Chem. Soc., 104, 6053-6060.
18. C.M. Cimarusti and R.B. Sykes, Chem. Brit., 302-302 (1983); Med. Chem. Rev., 4, 1-23 (1984).
19. T. Kamiya, H. Aoki and Y. Mine, in "Chemistry and Biology of β-Lactam Antibiotics", R.B. Morin and M. Gorman, eds., Academic Press, N.Y., vol. 2, 1982, pp. 165-226.
20. S. Kishimoto, M. Sendai, S. Hashiguchi, M. Tonimoto, Y. Satoh, T. Matsuo, M. Kondo and M. Ochiai, J. Antibiotics, 36, 1421-1424 (1983).
21. G.A. Koppel, L. McShane, P. Jose and R.D. Gooper, J. Am. Chem. Soc., 100, 3933-3935 (1978).
22. T. Kamiya, T.O. Ku, O. Nakaguchi, H. Takeno and M. Hashimoto, Tetrahedron Lett., 5119-5122 (1978); T. Kamiya, M. Hashimoto, O. Nakagochi and T. Oku, Tetrahedron, 35, 323-328 (1979).
23. H.H. Wasserman, D.L. Hlasta, A.W. Tremper and J.S. Wu, Tetrahedron Lett., 549-552 (1979).
24. P.G. Mattingly and M.J. Miller, J. Org. Chem., 46, 1557-1564 (1981).
25. C.A. Townsend and L.T. Nguyen, Tetrahedron Lett., 23, 4859-4862 (1982), J. Am. Chem. Soc., 103, 4582-4583 (1981).
26. D.P. Sahu, P. Mashawa, M.S. Manhao and A.K. Bose, J. Org. Chem., 48, 1144-1146 (1983).
27. O. Mitsunobu, Synthesis, 1-28 (1981).
28. M. J. Miller, P.G. Mattingly, M.A. Morrison and J.F. Kerwin, Jr., 102, 7026-7032 (1980).
29. A. Streitweiser, Jr., C.L. Wilkins and E.Kiehlman, J. Am. Chem. Soc., 90, 1598-1601 (1968); J.B. Hendrickson, D.D. Sternbach and K.W. Bair, Acc. Chem. Res., 10, 306-312 (1977).
30. S. Hanessian and J.-M. Vatèle, Tetrahedron Lett., 22, 3579-3582 (1981).
31. H.A. Staab, Angew. Chem., Int. Ed. Engl., 1, 351-367 (1962).
32. S. Hanessian, C. Couture and H. Wyss, unpublished results.
33. D. Kronenthal, C.Y. Han and M.K. Taylor, J. Org. Chem., 47, 2765-2768 (1982).
34. C. M. Cimarusti, H.E. Applegate, H.W. Chang, D.M. Floyd, W.H. Koster, W.A. Slusarchyk and M.G. Young, J. Org. Chem., 47, 180-182 (1982).
35. S. Hanessian, "Total Synthesis of Natural Products - The 'Chiron' Approach", J.E. Baldwin ed., Pergamon Press, Oxford, U.K., 1983.
36. S. Hanessian, D. Desilets, G. Rancourt and R. Fortin, Can. J. Chem., 60, 2292-2294 (1982); see also N. Ikota, D. Yushino, and K. Koga, Chem. Pharm. Bull., 30, 1929-1931 (1982); A. Knierzniger and A. Vasella, J.C.S. Chem. Comm., 9-11 (1984); P. Durette, Carbohydr. Res., 100, C27-C30 (1982).
37. C. M. Cimarusti, D. B. Bonner, H. Breuer, H.W. Chang, A.W. Fritz, D.M. Floyd, T.P. Kissack, W. H. Koster, D. Kronenthal, F. Massa, R.H. Mueller, J. Plusec, W.A. Slusarchyk, R.B. Sykes, M. Taylor and E.R. Weaver, Tetrahedron, 39, 2577-2589 (1983).

38. M.W. Whitehouse, P.W. Kent and C.A. Pasternak, J. Chem. Soc., 2315-2317 (1954).
39. S. Hanessian and S.P. Sahoo, Can. J. Chem., 62, 1400-1402 (1984).
40. S. Kobayashi, T. Timori, T. Izawa and M. Ohno, J. Am. Chem. Soc., 103, 2406 (1981).
41. For example, DCC; EDAC.HCl; EtMgBr; methanesulfonyl chloride, n-Bu_4NHSO_4; Mitsunobu contidions.
42. K. Drauz, A. Kleeman, and J. Martens, Angew. Chem., Int. Ed. Engl., 21, 584-608 (1982).