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Synthetic approaches to tetrahydroisoquinoline-3-carboxylic acid derivatives†

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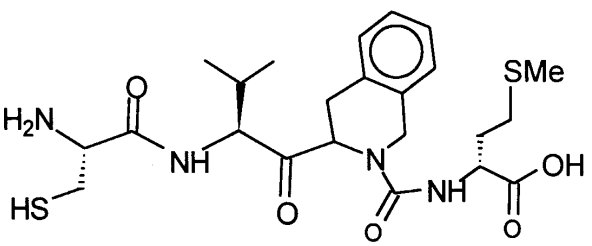
Abstract

Tetrahydroisoquinoline-3-carboxylic acid (Tic) is an important structural unit in many biologically active peptides. Various literature methods available for Tic preparation are described here.

Keywords: Tetrahydroisoquinoline, tetrahydroisoquinoline-3-carboxylic acid, peptide drugs, constrained amino acids.

1. Introduction

Several pharmacological properties such as metabolic instability and poor bioavailability of peptides preclude their usage as drugs. Most of the linear peptides isolated to date show lack of selectivity to one or other type of receptors as they are structurally flexible.[1–5] Generally adopted method for the development of peptide drugs involves the synthesis of conformationally restricted analogues that imitate the receptor-bound conformation of the endogenous ligands as closely as possible.[6] Several other possibilities also exist for the synthesis of conformationally restricted and metabolically stable peptides at the amino acid level.[7–8] These involve the systematic exchange of the individual amino acids with the synthetic (or unusual) amino acids with sterically demanding side chains.[9–10] Insertion of tetrahydroisoquinoline-3-carboxylic acid (Tic) in the second position of several opioid peptides has dramatic consequences of their activity and selectivity.[11] In connection with the design of topographically constrained peptides, Tic has been utilized in several instances as a replacement of Phe or tyrosine.[12–16] For example, in somatostain-derived μ-opioid antagonists these modifications led to a highly selective and potent peptides. Tic has been utilized in farnesyl inhibitors as a replacement of Phe (Fig. 1).[17] Introduction of Tic in didemnin B as a conformationally restricted replacement for tyrosine is shown to have comparable potency as a protein biosynthesis inhibitor.[18]



Farnesyl transeferase inhibitor containing Tic.

FIG.1.

†Dedicated to Prof. S. C. Bhattacharyya.
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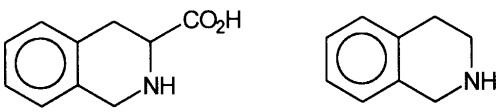
Tic provides two potential advantages for the replacement of Phe in bioactive peptide ligands. Conformational constraints are introduced in peptide backbone by the pipecolinic acid bridge and orientation of the aromatic side chain is restricted.[19–21] Moreover, 1,2,3,4-tetrahydroisoquinoline (THIQ) core (**2**) is an important structural element in several important alkaloids and other medicinally useful products.[22–25]



Tic (**1**) THIQ(**2**)

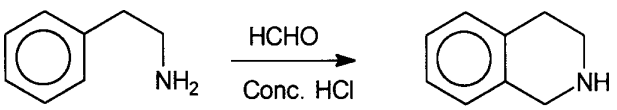
FIG. 2.

The availability of synthetic methods for the preparation of various Tic derivatives with varying degree of steric/electronic and hydrophobic properties is useful in receptor mapping and also in designing meaningful QSAR studies.[26]

2. Methods for the synthesis of Tic derivatives

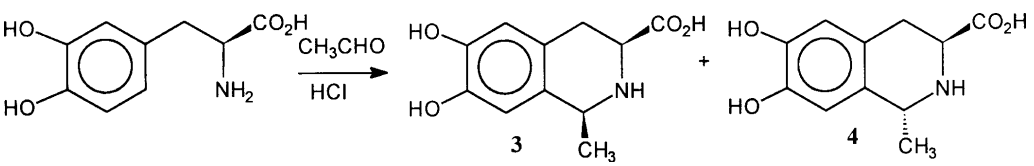
2.1. *Pictet–Spengler reaction*

In 1911, Pictet and Spengler reported[27] that the reaction of β-phenylethylamine with formaldehyde in the presence of conc. HCl gave THIQ (**2**) (Scheme 1).[28] It was immediately extended by Decker and Becker to the condensation of substituted phenethylamines with various aldehydes.[29,30] The first example of asymmetric synthesis of isoquinoline alkaloids performed with the use of natural amino acids was reported by Brossi *et al*. in 1972.



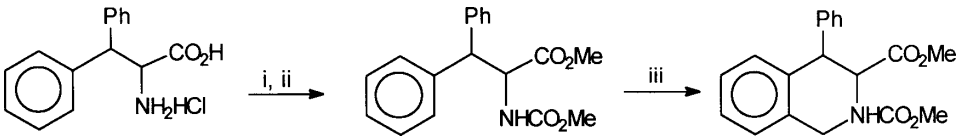
Scheme 1.

In a biomimetic type of process, a series of 3-carboxyl-substituted THIQ alkaloids have been prepared by treatment of L-Dopa with formaldehyde or acetaldehyde (Scheme 2) to give Tic derivatives **3** and **4**. Several groups have used this methodology to synthesize various Tic derivatives.



Scheme 2.

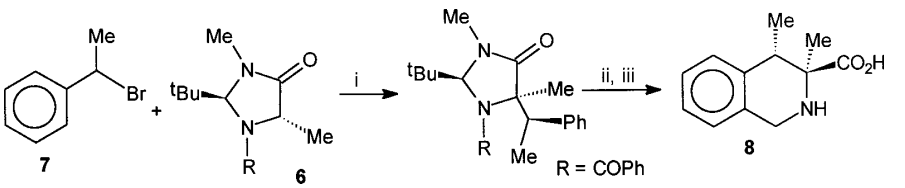
Recently, Chen and Goel reported the synthesis of 4-phenyl Tic derivatives by this methodology and the reaction is facilitated by the presence of electron-donating groups in the aromatic ring (Scheme 3).[31] The electron-withdrawing groups inhibit the reaction. Moreover, the relatively harsh dehydrating conditions (conc. HCl) necessary to form the THIQ ring system **2** is the limitation of this methodology.



Reagents: i) $ClCO_2Me$, 1M NaOH; ii) CH_2N_2 and iii) CH_2O/HCl.

Scheme 3.

Hruby and coworkers have reported the preparation of topographically constrained Tic derivatives such as α, β-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**8**) in high optical purity using Seebach's chiral glycine anion equivalent **6**. Alkylation of chiral auxiliary (**6**) with racemic (1-bromoethyl)benzene (**7**), and hydrolysis, followed by Pictet–Spengler cyclization reaction gave Tic derivative **8** (Scheme 4).[32]

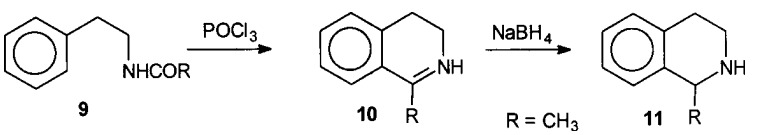


Reagents: i) LDA; ii) reflux in 6N HCl and iii) Pictet–Spengler cyclization.

Scheme 4.

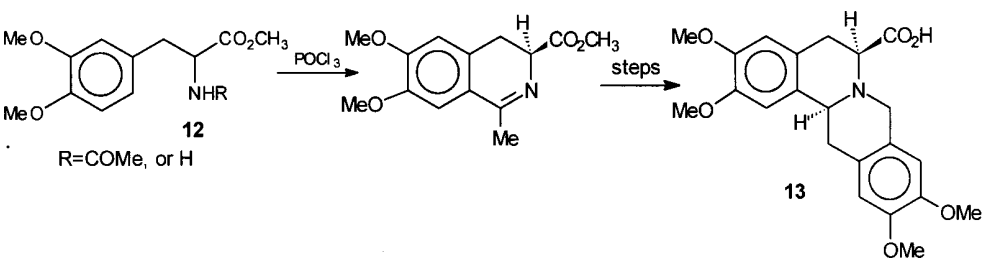
2.2. *Bischler–Napieralski reaction*[33]

This methodology involves the cyclodehydration of acyl derivative of β-phenethylamine (**9**) in the presence of Lewis acid such as phosphoryl choride or phosphorous pentoxide in an inert solvent to give 3,4-dihydroisoquinoline (**10**), which is then reduced to a THIQ system (**11**) (Scheme 5). Sodium borohydride in methanol or catalytic hydrogenation is routinely used for the reduction of **10**.



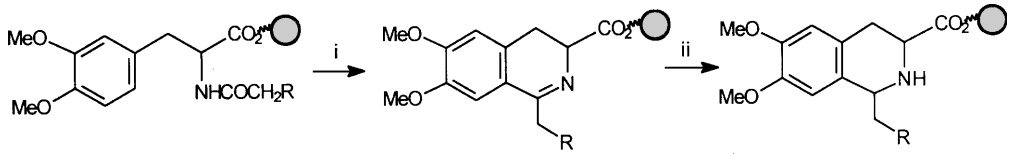
Scheme 5.

Kametani *et al*.[34] reported the synthesis of (*S*)-xylopinine (**13**) starting from **12** via Bischler–Napieralski reaction as a key step (Scheme 6).



Scheme 6.

Recently, Meutermans and Alewood[35] reported the synthesis of dihydro and tetrahydroisoquinoline-3-carboxylic acid derivatives via Bischler–Napieralski reaction by solid-phase synthesis using Merrifield resin (Scheme 7).

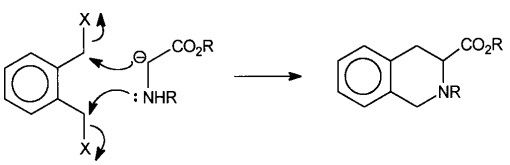


Reagents: i) $POCl_3$, toluene/80°C and ii) $NaCNBH_3$/MeOH/HCl.

Scheme 7.

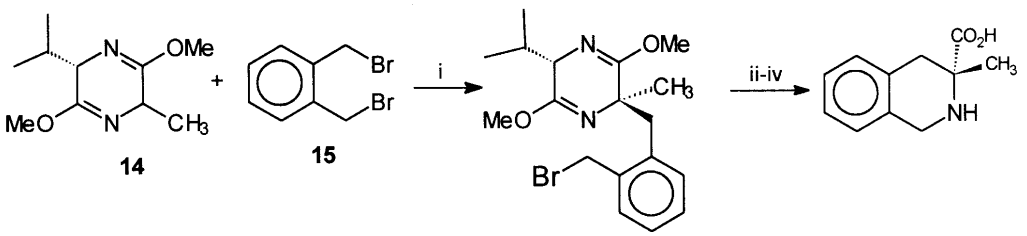
2.3. *Approaches based on glycine equivalents*

Strategically, *C*- and *N*-alkylations of glycine derivatives either simultaneously or in a stepwise fashion with a suitably substituted benzene derivatives can generate the Tic moiety (Scheme 8). Here, we describe various tactics that utilize this concept for the preparation of Tic derivatives. These methods are strategically different from the Pictet–Spengler and Bischler–Napieralski reactions in the sense that these two methods start with phenylalanine derivatives whereas the glycine method involves functionalization of glycine derivatives with a suitable aromatic substrate. Moreover, electrophilic cyclization on the aromatic ring is avoided, thereby providing a better scope for the introduction of the electron-withdrawing substituents in the aromatic ring.



Scheme 8.

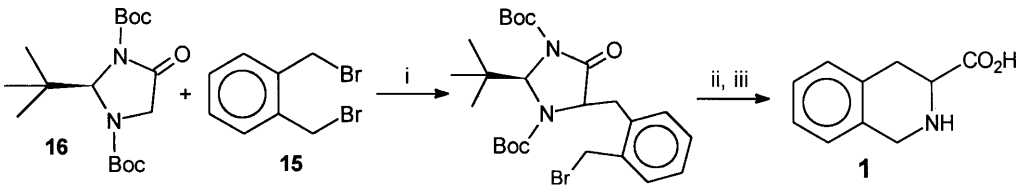
In 1987, Schöllkopf and coworkers have reported the synthesis of optically active Tic derivatives using bis-lactum ether (**14**) as a glycine equivalent.[36] The commercially available bis-lactum ether (**14**) has been alkylated with α,α'-dibromo-*o*-xylene (**15**) in a stepwise manner under different reaction conditions to give optically pure Tic derivatives (Scheme 9).



Reagents: i) *n*-BuLi, –78°C/THF; ii) Nal/DMF; iii) HBr/EtOH and iv)EtOH/propylene oxide.

Scheme 9.

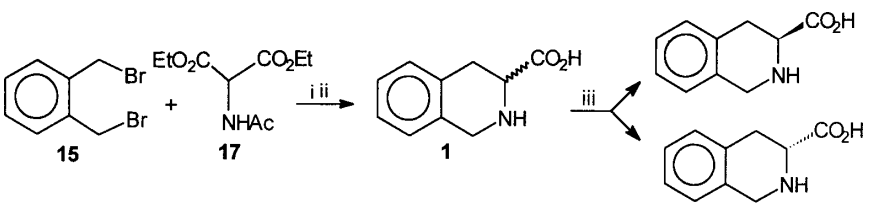
Later on, Seebach and coworkers have reported the optically pure Tic derivatives using Boc-protected chiral synthon.[37] The alkylation of Boc-protected chiral auxiliary **16** with dibromo-*o*-xylene (**15**) followed by *N*-cyclization and subsequent hydrolysis gave optically pure Tic derivatives (Scheme 10).



Reagents: i) LDA/THF; ii) Na_2CO_3, NaI/CH_3CN and iii) H^+.

Scheme 10.

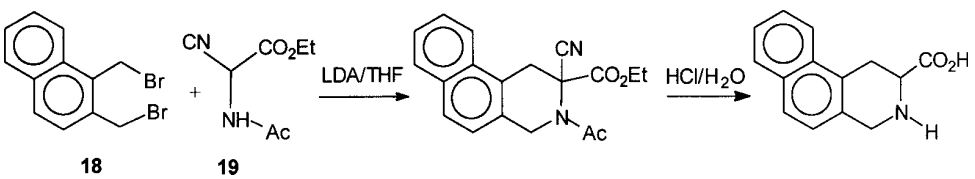
Kammermeier *et al.*[38] reported an efficient synthesis of racemic Tic (**1**) using base-catalyzed cyclization of diethyl acetamidomalonate (**17**) with dibromo-*o*-xylene (**15**) as a key step. Thus, dibromo-*o*-xylene (**15**) on condensation with **17** in refluxing methanol followed by hydrolysis gave racemic Tic which was resolved via diasteriomeric separation. Here (–)-menthol is used as a resolving agent (Scheme 11).



Reagents: i) NaOMe/MeOH, ii)KOH/MeOH/H_2O and iii) Resolution.

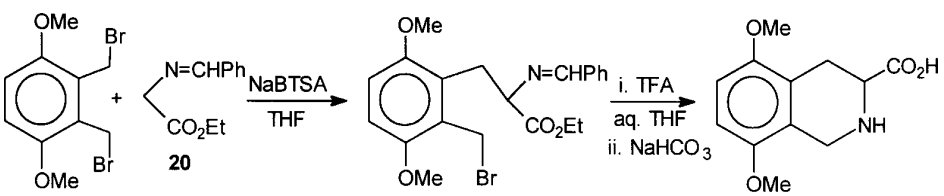
Scheme 11.

In a study aimed at preparing the topographically constrained AAA derivatives, Wang and Moseberg[39] reported benzo-annulated Tic derivatives via base-catalyzed condensation of 1,2-di(bromomethyl)naphthalene (**18**) with ethyl acetamidocyanoacetate (**19**). A representative example of this strategy is shown in Scheme 12.



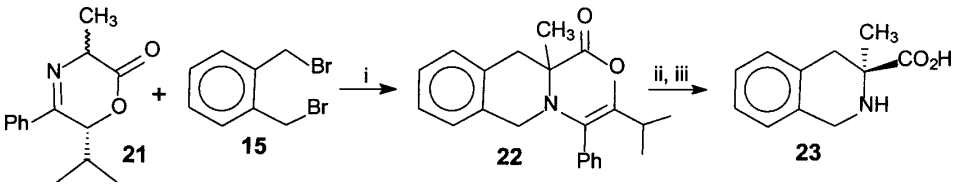
Scheme 12.

Mash *et al.*[40] reported the synthesis of Tic derivatives from α,α'-dibromo-*o*-xylene derivatives via a sequential *C*- and *N*-alkylations of glycine derivative (**20**). The general theme of this method is shown in Scheme 13. It is important to note that this method tolerates electron-donating substituents in the aromatic portion of the target molecule.



Scheme 13.

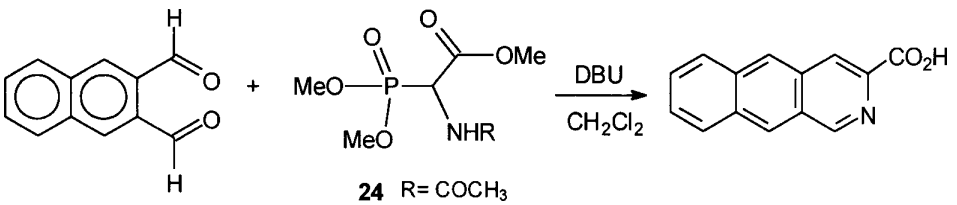
In 1999, Najera and coworkers[41] have reported the synthesis of 3-methyl Tic derivatives using diastereoselective alkylation of chiral auxilliary (**21**) with dibromide (**15**) under phase transfer catalysis conditions (tetrabutylammonium bromide, TBAB) to give the tricyclic system (**22**) which on hydrolysis delivered enantiomerically pure Tic derivative (**23**) (Scheme 14).



Reagents: i) K_2CO_3, TBAB; ii) HCL Δ, and iii) propylene oxide.

Scheme 14.

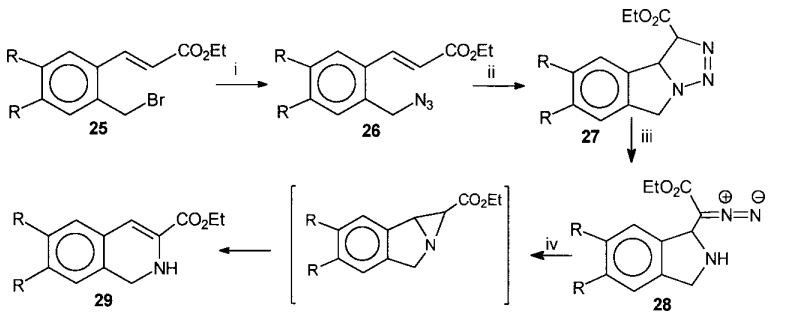
Hiebl *et al.*[42] have reported a novel and general methodology for the synthesis of various isoquinoline derivatives using Cbz-phosphonoglycine methyl ester as a glycine equivalent. Here, *C*- and *N*-alkylations occur simultaneously. Thus, Wittig–Horner reaction of *o*-phthalaldehydes with *N*-acetylphosphonoglycine (**24**) in the presence of DBU gave various isoquinoline derivatives in good yield (Scheme 15). It should be noted that this methodology provides various isoquinoline derivatives with electron-withdrawing groups in the benzene ring and it was also extended to various heterocyclic 1,2-dialdehydes.



Scheme 15.

2.4. *Cycloaddition approaches*

Sha and coworkers[43] have reported the synthesis of functionalized 1,2-dihydroisoquinoline derivatives by intramolecular 1,3-dipolar cycloaddition of alkyl azides and olefins. A schematic representation of this idea is depicted in Scheme 16. Reaction of bromide **25** with sodium azide

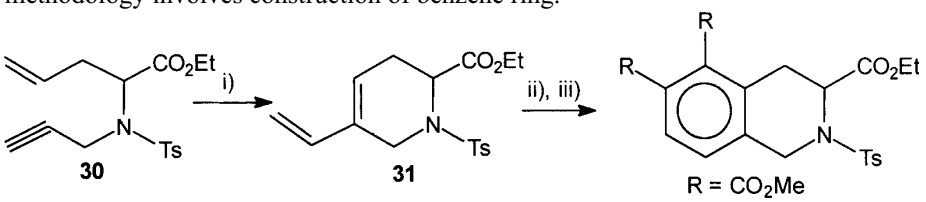


Reagents: i) NaN_3; ii) NBS; iii) silica gel/Δ, 60–70°C and iv) rhodium acetate.

Scheme 16.

afforded azido derivative (**26**), which on 1,3-dipolar cycloaddition intramolecularly gave triazoline (**27**). Rearrangement of **27** on silica gel gave diazo compound (**28**), which on reaction with rhodium acetate afforded substituted 1,2-dihydroisoquinoline-3-carboxylic acid derivatives such as **29**.

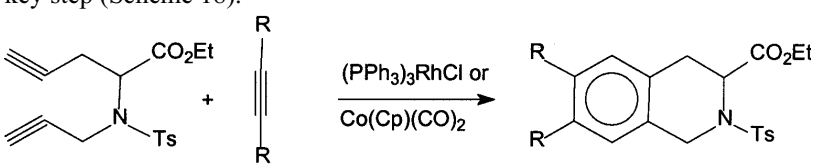
Kotha *et al*.[44] reported a novel synthesis of highly functionalized Tic derivatives using enyne metathesis reaction and Diels–Alder reaction as key steps (Scheme 17). The *N*-alkylated enyne building blocks (**30**) were synthesized from benzophenone Schiff base which upon enyne metathesis in the presence of Grubb's catalyst gave heterocyclic inner-outer ring diene (**31**), a useful precursor for the construction of Tic derivatives, via Diels–Alder approach. This methodology is conceptually new from the conventional Pictet–Spengler and Bischler–Napierlasky reaction methods because the latter methods start from the preformed benzene derivatives and the present methodology involves construction of benzene ring.



Reagents: i) Grubbs catalyst [(PhCH=$RuCl_2(PCy_3)_2$]; ii) dienophile/Δ and iii) DDQ, benzene reflux.

Scheme 17.

In connection with the building block approach[45–63] for the first time, Kotha *et al*.[64] developed a new methodology for the synthesis of Tic derivatives via [2+2+2]cycloaddition reaction as a key step (Scheme 18).



R = CH_2OH, CO_2Me, Ph, TMS,

Scheme 18.

3. Conclusions

Since Tic is an important structural element in many biologically active molecules, there is a need to develop new methods for its preparation.[64–70] Synthetic methods starting with preformed benzene derivatives are very simple and straightforward. However, these methods tolerate only a limited number of functional groups in the aromatic ring. Cycloaddition strategies for Tic preparation exhibit a greater scope in terms of generating diverse functional groups in the aromatic ring. Methods based on organometallic reagents are likely to appear for Tic assembly in the near future.

Acknowledgements

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References

1. Gunte, J. *Angew. Chem., Int. Engl. Ed.,* 1994, **33**, 1699.

2. Liskamp, R. M. J. — *Angew. Chem., Int. Engl. Ed.*, 1994, **33**, 633.
3. Schiller, P. W. — In *The peptides: Analysis, synthesis, biology,* Vol. 6 (Udenfriend, S. and Meienhofer, J., eds), Academic Press, 1984, pp. 219–268.
4. Giannis, A. and Koter, T. — *Angew. Chem.*, *Int. Engl. Ed.,* 1993, **32**, 1244.
5. Hruby, V. J. — *Biopolymers,* 1993, **33**, 1073.
6. Ortwine, D. F. *et al.* — *J. Med. Chem.,* 1992, **35**, 1345.
7. Liskamp, R. M. J. — *Recl. Trav. Chim.*, *Pays-Bas*, 1994, **113**, 1.
8. Gibson, S. E., Guillo, N. and Tozer, M. J. — *Tetrahedron,* 1999, **55**, 585.
9. Hruby, V. J., Cody, W. L., Castrucci, A. M. D. and Hadley, M. E. — *Collect. Czech. Chem. Commun*., 1988, **53**, 2549.
10. Ornstein, P. L. *et al.* — *J. Med. Chem.,* 1992, **35**, 3547.
11. Shiller, P. W. *et al.* — *Proc. Natn. Acad. Sci. USA,* 1992, **89**, 11871.
12. Kazmierski, W. M., Yamamura, H. I. and Hruby, V. J. — *J. Am. Chem. Soc*., 1991, **113**, 2275.
13. Mosberg, H. I. *et al.* — *J. Med. Chem*., 1994*,* **37**, 4371.
14. Koerber, S. C., Ibea, M., Hagler, A. T., Rivier, C. L. and Rivier, J. E. — *Biochem. Biophys. Res. Commun.,* 1992**, 187**, 1035.
15. Kazmierski, W. M., Urbanczyk-Lipkowska, Z. and Hruby, V. J. — *J. Org. Chem.,* 1994, **59**, 1789.
16. Tancredi, T. *et al.* — *Eur. J. Biochem*., 1994, **224**, 241.
17. Clerc, F. F. *et al.* — *Bioorg. Med. Chem. Lett.,* 1995, **5**, 1779.
18. Pfizenmayer, A. J. *et al*. — *Bioorg. Med. Chem. Lett*., 1998, **8**, 3653.
19. Keseler, H., Kuhn, M. and Loschner, T. — *Liebigs Ann. Chem*., 1986, 1.
20. Ornstein, P. C. *et al.* — *J. Med. Chem.,* 1991, **34**, 90.
21. Hays, S, J., Malone, T. C. and Johnson, G. — *J. Org. Chem*., 1991, **56**, 4084.
22. Kametani, T. — The total synthesis of isoquinoline alkaloids. In *The total synthesis of natural products,* Vol. 3 (ApSimon, J., ed), Wiley, 1977, pp. 1–272.
23. Bently, K. W. — *The isoquinoline alkaloids*, Harwood Academic, 1998.
24. Rozwadowska, M. D. — *Heterocycles,* 1994, **39**, 903.
25. Grunewald, G. L., Caldwell, T. M., Li, Q. and Criscione, K. R. — *Bioorg. Med. Chem*., 1999, **7**, 869.
26. Griffiths, E. C. — In *A textbook of drug design and development* (P. Krogsgaard–Larsen, and H. Bundgaard, eds), Harwood Academic, 1992, pp. 487–528.
27. Pictet, A. and Spengler, T. — *Ber.*, 1911, **44**, 2030.
28. Decker, H. and Becker, P. — *Annalen*, 1913, **395**, 342.

29. Brossi, A., Focella, A. and Teitel, S. *Helv. Chim. Acta,* 1972, **55**, 15.
30. Kahno, H. and Sekine, Y. *Heterocycles,* 1996, **42**, 141.
31. Chen, H. G. and Goel, O. P. *Synth. Commun.,* 1995, **25**, 49.
32. Kazmierski, W. M. and Hruby, V. J. *Tetrahedron Lett.,* 1991, **32**, 5769.
33. Whaley, W. M. and Govindachari, T. R. *Org. React.,* 1951, **6**, 74.
34. Kametani, T., Takagi, N., Toyota, M., Honda, T. and Fukumoto, K. *Heterocycles,* 1981, **16**, 591.
35. Meutermans, W. D. F. and Alewood, P. F. *Tetrahedron Lett.,* 1995, **36**, 7709.
36. Schöllkopf, U., Hinrchs, R. and Lonsky, R. *Angew. Chem., Int. Engl. Ed.,* 1987, **26**, 143.
37. Seebach, D., Dziadulewicz, E., Behrendt, L., Cantoreggi, S. and Fitzi, R. *Liebigs Ann. Chem.,* 1989, 1215.
38. Kammermeier, T., Lerch, U. and Sommer, C. *Synthesis,* 1992, 1157.
39. Wang, C. and Moseberg, H. I. *Tetrahedron Lett.,* 1995, **36**, 3623.
40. Mash, E. A., Williams, L. J. and Pfeiffer, S. S. *Tetrahedron Lett*., 1997, **38**, 6977.
41. Chinchilla, R., Galindo, N. and Najera, C. *Synthesis,* 1999, 704.
42. Hiebl, J. *et al*. *Tetrahedron Lett.,* 1999, **40**, 7935.
43. Liu, J. M., Young, J. J., Li, Y. J. and Sha, C. K. *J. Org. Chem.,* 1986, **51**, 1120.
44. Kotha, S. and Sreenivasachary, N. *Chem. Commun.,* 2000, 503.
45. Kotha, S., Sreenivasachary, N. and Brahmachary, E. *Tetrahedron Lett*., 1998, **39**, 2805.
46. Kotha, S., Brahmachary, E. and Sreenivasachary, N. *Tetrahedron Lett*., 1998, **39**, 4095.
47. Kotha, S. and Brahmachary, E. *Tetrahedron Lett*., 1997, **38**, 3561.
48. Kotha, S. and Brahmachary, E. *Bioorg. Med. Chem. Lett*., 1997, **7**, 2719.
49. Kotha, S. and Brahmachary, E. *Tetrahedron Lett*., 1997, **38**, 9031.
50. Kotha, S. and Brahmachary, E. *J. Org. Chem.,* 2000, **65**, 1359.
51. Kotha, S., Sreenivasachary, N. and Halder, S. *Bioorg. Med. Chem. Lett*., 1999, **9**, 2565.
52. Kotha, S. and Sreenivasachary, N. *Bioorg. Med. Chem. Lett*., 1998, **8**, 257.
53. Kotha, S., Halder, S. Brahmachary, E. and Ganesh, T. *Synlett,* 2000, 853.
54. Kotha, S., Ganesh, T. and Ghosh, A. K. *Bioorg. Med. Chem. Lett*., 2000, **10**, 1755.
55. Kotha, S., Mohanraj, K. and Durani, S *Chem. Commun.,* 2000,1909.

56. Kotha, S., Sreenivasachary, N. and Brahmachary, E. *Eur. J. Org. Chem.*, 2001, 787.

57. Kotha, S. and Brahmachary, E. *Indian J. Chem. B,* 2001, **40**, 1.

58. Kotha, S., Sreenivasachary, N. and Brahmachary, E. *Tetrahedron*, 2001, **57**, 6261.

59. Damodaran, L., Mohanraja, K., Kotha, S. and Pattabhi, V. *Biopolymers*, 2001, **59**, 330.

60. Kotha, S. and Sreenivasachary, N. *Eur. J. Org. Chem*., 2001, 3375.

61. Kotha, S., Sreenivasachary, N., Mohanraja, K. and Durani, S. *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1421.

62. Kotha, S. and Lahiri, K. *Bioorg. Med. Chem. Lett.,* 2001, **11**, 2887.

63. Kotha, S., Behera, M. and Vinod Kumar, R. *Bioorg. Med. Chem. Lett.* (submitted)

64. Kotha, S. and Sreenivasachary, N. *Bioorg. Med. Chem. Lett.,* 2000, **10**, 1413.

65. Brozda, D., Koroniak, L. and Rozwadowska, M. D. *Tetrahedron: Asymmetry,* 2000, **11***,* 3017.

66. Santagada, V. *et al.* *Tetrahedron Lett.,* 2001, **42**, 3507.

67. McKenna, J. M., Moliterni, J. and Qiao, Y. *Tetrahedron Lett.,* 2001, **42**, 5797.

68. Katritzky, A. R., He, H-Y. and Long, Q. *Tetrahedron: Asymmetry,* 2001, **12**, 2427.

69. Spengler, J. *et al*. *Synthesis*, 2001, 1513.

70. Lazarus, L. H. *et al.* *Drug Discovery Today*, 1998, **3**, 284.