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**DIVERSITY-ORIENTED APPROACH TO 1,2,3,4-TETRAHYDROISO-
QUINOLINE-3-CARBOXYLIC ACID (TIC) DERIVATIVES USING
DIETHYL ACETAMIDOMALONATE AS A GLYCINE EQUIVALENT :
FURTHER EXPANSION BY SUZUKI-MIYaura CROSS-COUPPLING
REACTION†**

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Abstract – Synthesis of diverse 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
(Tic) derivatives and its higher analogues are reported using diethyl
acetamidomalonate as a glycine equivalent. In addition, various substituted Tic
derivatives are assembled by application of Suzuki–Miyaura cross-coupling
reaction as a key step.

Constrained α -amino acid (AAA) derivatives play a critical role in the design of biologically active peptides and peptidomimetics.¹ 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (Tic) is considered as a constrained analogue of phenylalanine (Phe), where its dihedral angle is limited to a small range ($\chi = +60^\circ$, -60°).² In addition, Tic has also been employed as a useful building block for the synthesis of various biologically active alkaloid derivatives.³ Peptides containing Tic are also used as δ -opioid receptor antagonists.⁴ Interestingly, the Tic residue adopts different conformations depending on whether it is incorporated at the *N*-terminus or at a central location of the peptide chain. Recent studies indicate that by incorporation of Tic residues, the resulting peptide can adopt both helical and β -bonded structures. Generally, Tic derivatives are assembled by Pictet–Spengler or Bischler–Napieralski reactions as a key step.⁵ In order to expand the synthetic routes to Tic derivatives, development of other approaches is desirable.⁶ In connection with the studies related to the bioactive conformation of peptide

† This paper is dedicated to Emeritus Professor Akira Suzuki on the occasion of his 80th birthday

ligands, various Tic derivatives were assembled (Figure 1).⁷ In continuation of our efforts to design various Tic derivatives by a building block approach,¹¹ we conceived a general strategy to several Tic derivatives involving diethyl acetamidomalonate (DEAM) as a glycine equivalent. Although DEAM is used for the construction of various unusual amino acid derivatives, its utility towards the preparation of Tic derivatives however is less explored.¹²

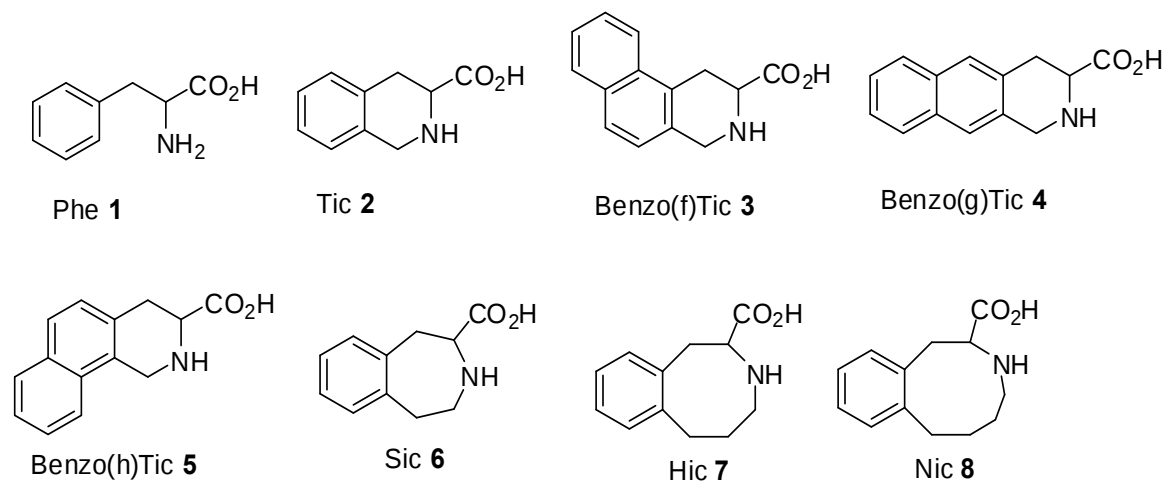
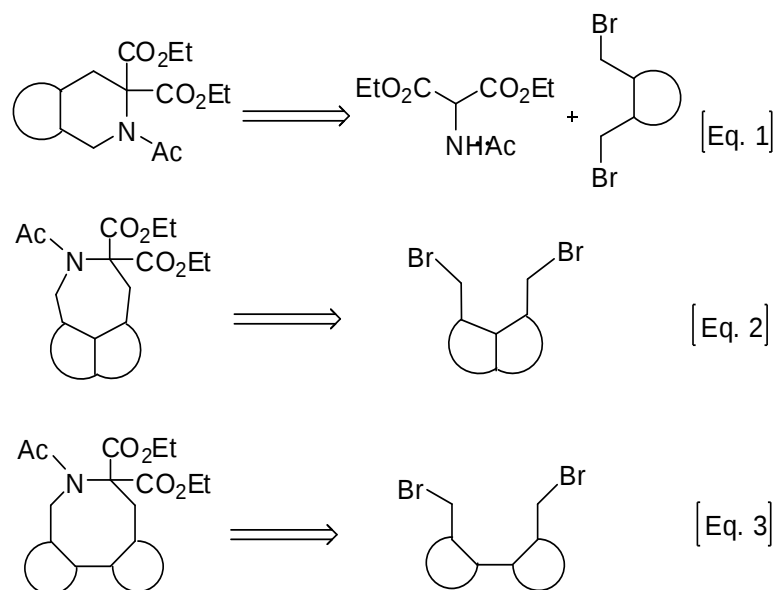


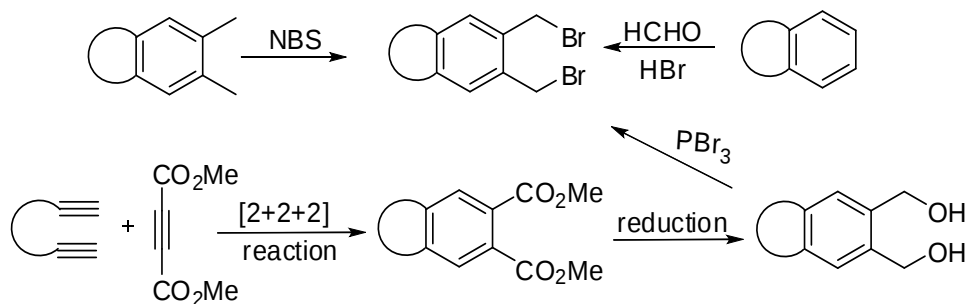
Figure 1. Various constrained AAA derivatives related to Tic

Here we describe the synthesis of various Tic derivatives, by treating α,α' -dibromo-*o*-xylenes, with DEAM in presence of a mild base such as K_2CO_3 (Scheme 1). By choosing an appropriate dibromo derivative one can prepare Tic and its higher analogues (Eq. 1 – Eq. 3).



Scheme 1. Retrosynthetic approach to Tic and its higher analogues

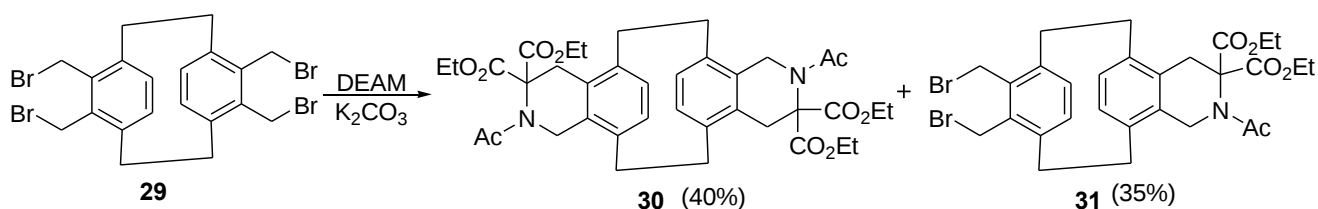
The required dibromo derivatives can be obtained from the corresponding dimethyl aromatic compounds with the aid of benzylic bromination using *N*-bromosuccinimide (NBS)¹³ under free radical condition or by bromination of the corresponding diols with PBr_3 (Scheme 2).¹⁴ The required diols were assembled by a [2+2+2]cycloaddition reaction and reduction as key steps.¹⁵ Alternatively, a bromomethylation¹⁶ strategy can also be adopted for this purpose.



Scheme 2. Synthetic approaches to α,α' -dibromo-*o*-xylene derivatives

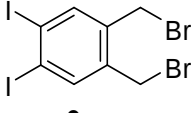
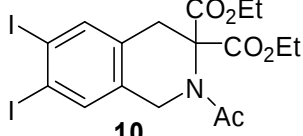
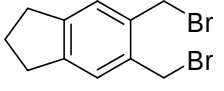
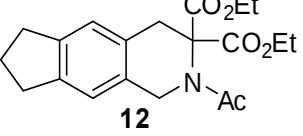
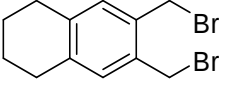
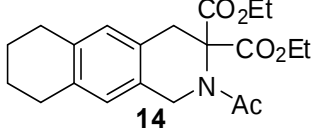
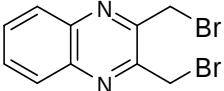
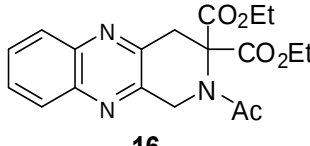
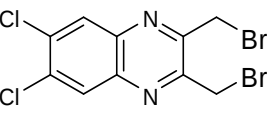
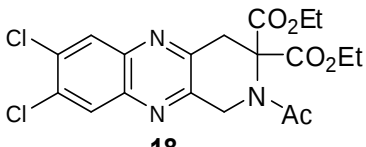
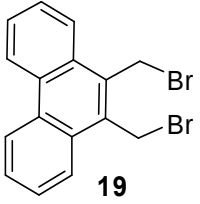
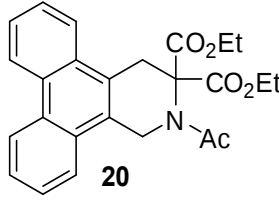
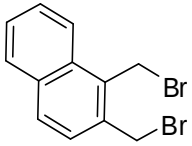
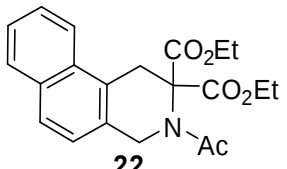
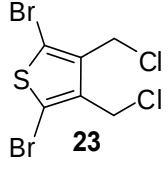
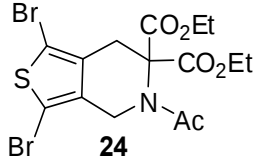
Reaction of α,α' -dibromo-*o*-xylene derivatives (Table 1) with DEAM in presence of K_2CO_3 gave various Tic derivatives in moderate yields. In a typical experimental procedure, a solution of dibromide (1 equivalent) in dry acetonitrile was treated with DEAM (1.1 equivalent), powdered potassium carbonate (6 equivalents) and tetrabutylammonium hydrogen sulfate (0.2 equivalent) as a phase-transfer catalyst. At the conclusion of the reaction (TLC monitoring), the reaction mixture was passed through a small pad of celite. The filtrate was concentrated and extracted with ethyl acetate (3×25 mL). The crude product obtained was purified by silica-gel column chromatography. Elution of the column with ethyl acetate-petroleum ether mixture furnished the required Tic derivative.

This methodology was also extended for the synthesis of higher analogues of Tic. Towards the preparation of Sic derivative **26**, the required dibromide was prepared from the corresponding anhydride.¹⁷ Later, treatment of the dibromide **25** with DEAM in the presence of K_2CO_3 gave Sic derivative **26**. Along similar lines, Hic derivative **28** was assembled starting with the commercially available 2,2'-bis(bromomethyl)-1,1'-biphenyl **27** (Table 2).



Scheme 3. Cyclophane based Tic derivative

Table 1. Preparation of various Tic derivatives

entry	starting material	product	condition	yield (%)
1	 9	 10	A	41
2	 11	 12	B	42
3	 13	 14	B	42
4	 15	 16	B	75
5	 17	 18	B	72
6	 19	 20	A	45
7	 21	 22	B	48
8	 23	 24	B	56

^aConditions A: DEAM (1 equiv.), K₂CO₃ (5 equiv.), MeCN reflux, 24 h.

Conditions B: DEAM (1.1 equiv.), K₂CO₃ (6 equiv.), TBAHS (0.2 equiv.), MeCN reflux, 20-22 h.

Table 2. Preparation of Sic and Hic derivatives

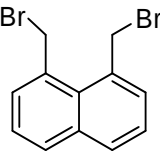
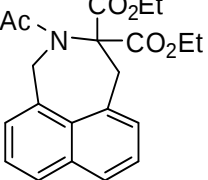
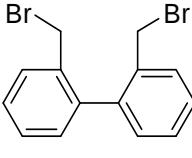
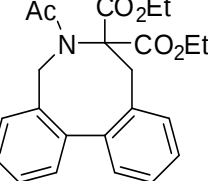
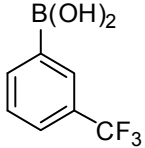
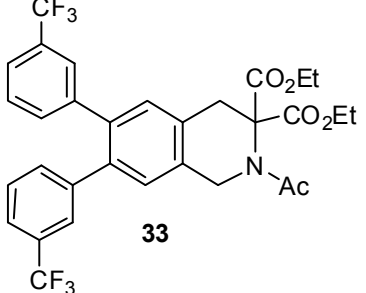
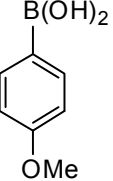
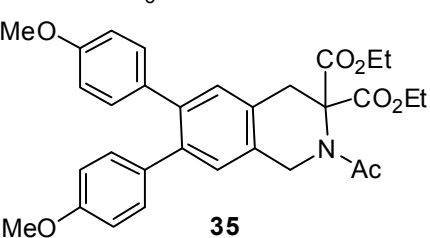
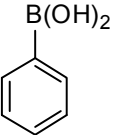
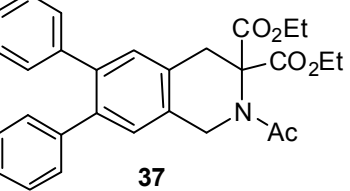
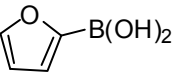
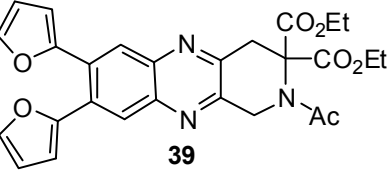
entry	starting material	product	condition ^a	yield (%)
1	 25	 26	A	64
2	 27	 28	A	64

Table 3. Expansion of Tic derivatives by Suzuki cross-coupling reaction

entry	substrate	boronic acid	product	condition ^a	yield (%)
1	10	 32	 33	A	35
2	10	 34	 35	A	49
3	10	 36	 37	A	30
4	18	 38	 39	B	37

^aConditions A: [Pd₂(dba)₃], Buchwald Ligand (5 mol%), Na₂CO₃, THF/toluene/H₂O, 70 °C.

Conditions B: [Pd₂(dba)₃], LiCO₃, dioxane:H₂O (3:1), MW, 5 min.

It is interesting to note that this strategy could also be extended to cyclophane derivative **29**. Accordingly, when tetrabromide **29**¹⁸ was reacted with DEAM under the above condition to give di-Tic derivative **30** along with mono-Tic derivative **31** in 40% and 35% yields, respectively. The regiochemistry of compound **30** has been established by single crystal X-ray diffraction analysis.¹⁹ In view of various recent applications of [2.2] paracyclophane chemistry these results may found useful application in bioorganic chemistry.²⁰

Having prepared various Tic derivatives and its higher analogues, diiodo Tic derivative **10** was chosen as a suitable precursor to realize the Suzuki–Miyaura (SM) cross-coupling step. We found that the corresponding tetrabromo derivative is not a friendly precursor. To this end, we prepared various SM cross-coupling products by reaction of **10** with various boronic acids under Pd catalyst conditions. Several derivatives prepared by SM coupling reaction are included in Table 3.

In a typical reaction procedure, the diiodo Tic derivative **10** was reacted with an appropriate boronic acid, THF/toluene/H₂O (1:1:1) in presence of Na₂CO₃, at 70 °C for 15-20 min followed by addition of [Pd₂(dba)₃] (1.5 mol%) and Buchwald ligand²¹ (5 mol%) (condition A). At the end of the reaction (TLC monitoring), the reaction mixture was concentrated and the crude product obtained was purified by silica-gel column chromatography. Elution of the column with an ethyl acetate-petroleum ether mixture gave the cross-coupling product. In some cases, the SM cross-coupling reaction was also carried out in the absence of a ligand by using [Pd₂(dba)₃] (1.5 mol%), dioxane:H₂O = 3:1) in the presence of LiCO₃ under microwave irradiation (condition B). All new compounds were characterized on the basis of high resolution ¹H NMR and mass spectral data.

In conclusion, we have shown that DEAM is a useful glycine equivalent to prepare diverse Tic derivatives under mild reaction conditions. Further, we have shown that SM cross-coupling reaction is useful to generate various functionalized Tic derivatives. Since a large number (>900) of boronic acids are commercially available, the present strategy can be easily extended to generate a library of Tic derivatives by applying SM cross-coupling reaction. Since the development of new synthetic methods for the preparation of unusual AAA derivatives is important for designing peptide-based drugs, our methodology may be of interest to medicinal and bioorganic chemists.

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REFERENCES

1. M. Zheng, X. Zhang, M. Zhao, H. W. Chang, W. Wang, Y. Wang, and S. Peng, *Bioorg. Med. Chem.*, 2008, **16**, 9574.
2. I. Torrini, G. P. Zecchini, M. P. Paradisi, G. Lucente, G. Mastropietro, E. Gavuzzo, F. Mazza, and G. Pochetti, *Tetrahedron*, 1998, **54**, 165.
3. S. E. Gibson, N. Guillo, S. B. Kalindjian, and M. J. Tozer, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1289; S. E. Gibson, N. Guillo, J. O. Jones, I. M. Buck, S. B. Kalindjian, S. Roberts, and M. J. Tozer, *Eur. J. Med. Chem.*, 2002, **37**, 379; J. Yang, W. Y. Hua, F. X. Wang, Z. Y. Wang, and X. Wang, *Bioorg. Med. Chem.*, 2004, **12**, 6547; B. H. Hirth, S. Qiao, L. M. Cuff, B. M. Cochran, M. J. Pregel, J. S. Gregory, S. F. Sneddon, and J. L. Kane, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2087; H. Zhang, D. E. Zembower, and Z. Chen, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2687.
4. S. Ballet, D. Feytens, R. D. Wachter, M. D. Vlaeminck, E. D. Marczak, S. Salvadori, C. D. Graaf, D. Rognan, L. Negri, R. Lattanzi, L. H. Lazarus, D. Tourwé, and G. Balboni, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 433.
5. A. Pictet and T. Spengler, *Ber.*, 1911, **44**, 2030; W. M. Whaley and T. R. Govindachari, *Org. React.*, 1951, **6**, 74.
6. S. Kotha and N. Sreenivasachary, *J. Indian Inst. Sci.*, 2001, **81**, 277 and references cited therein; P. H. Dixneuf, G. T. Shchetnikov, S. N. Osipov, and C. Bruneau, *Synlett*, 2008, 578; T. Ooi, M. Takeuchi, and K. Maruoka, *Synthesis*, 2001, 1716; C. Wang and H. I. Mosberg, *Tetrahedron Lett.*, 1995, **36**, 3623; S. Azukizawa, M. Kasai, K. Takahashi, T. Miike, K. Kunishiro, Kanda, C. Mukai, and H. Shirahase, *Chem. Pharm. Bull.*, 2008, **56**, 335; K. V. Rompaey, I. V. D. Eynde, N. De Kimpe and D. Tourwé, *Tetrahedron*, 2003, **59**, 4421.
7. S. E. Gibson, N. Guillo, R. J. Middleton, A. Thulliez, and M. J. Tozer, *J. Chem. Soc., Perkin Trans. 1*, 1997, 447.
8. S. Kotha and N. Sreenivasachary, *Chem. Commun.*, 2000, 503; S. Kotha and N. Sreenivasachary, *Eur. J. Org. Chem.*, 2001, 3375; S. Kotha and P. Khedkar, *Synthesis*, 2008, 2925; S. Kotha, M. Meshram, and A. Tiwari *Chem. Soc. Rev.*, 2009, **38**, 2065; S. Kotha, K. Lahiri, D. Kashinath, and R. B. Sunoj, *Eur. J. Org. Chem.*, 2004, 4003; S. Kotha and K. Lahiri, *Eur. J. Org. Chem.*, 2007, 1221.
9. S. Kotha and N. Sreenivasachary, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1413; S. Kotha, E. Brahmachary, and K. Lahiri, *Eur. J. Org. Chem.*, 2005, 4741.
10. S. Kotha and S. Banerjee, *Synthesis*, 2007, 1015.
11. S. Kotha, *Acc. Chem. Res.*, 2003, **36**, 342.
12. B. O. T. Kammermeier, U. Lerch, and C. Sommer, *Synthesis*, 1992, 1157.
13. R. P. Kreher and T. Hildebrand, *Chem. Ber.*, 1988, **121**, 81.

14. R. H. Mitchell and F. Sondheimer, [*Tetrahedron*, 1968, **24**, 1397](#); J. Kenner and E. G. Turner, [*J. Chem. Soc.*, 1911, **99**, 2101](#); B. Saroja and P. C. Srinivasan, [*Tetrahedron Lett.*, 1984, **25**, 5429](#);
For substrate **15** and **17** see reference V. P. Ruggli, *Helv. Chim. Acta*, 1946, 2995.
15. S. Kotha and P. Khedkar, [*J. Org. Chem.*, 2009, **74**, 5667](#).
16. V. P. Kreher and N. Kohl, *Chemiker-Zeitung*, 1986, **110**, 299.
17. V. Boekelheide and G. K. Vick, [*J. Am. Chem. Soc.*, 1956, **78**, 653](#).
18. H. Hopf, I. Böhm, and J. Kleinschroth, *Org. Synth.*, 1990, **7**, 485.
19. S. Kotha, S. Misra, H. Hopf, and S. M. Mobin, unpublished results.
20. S. Kotha and S. Halder, *Arkivoc* (iii), 2005, 56; S. Kotha, S. Halder, L. Damodharan, and V. Pattabh, [*Bioorg Med. Chem. Lett.*, 2002, **12**, 1113](#); S. Kotha and K. Mandal, [*Adv. Synth. Catal.*, 2005, 1215](#); S. Kotha and K. Mandal, [*Eur. J. Org. Chem.*, 2006, 5387](#); A. Petler, R. A. C. N. Crump, and H. Kidwell, [*Tetrahedron Lett.*, 1996, **37**, 1273](#); A. de Meijere and B. König, [*Synlett*, 1997, 1221](#).
21. X. Huang, K. W. Anderson, D. Zin, L. Jiang, A. Klapars, and S. L. Buchwald, [*J. Am. Chem. Soc.*, 2003, **125**, 6653](#).