A new synthetic approach to 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) derivatives *via* enyne metathesis and the Diels–Alder reaction

Sambasivarao Kotha* and Nampally Sreenivasachary

Department of Chemistry, Indian Institute of Technology-Bombay, Mumbai, 400 076, India.
E-mail: srk@ether.chem.iitb.ernet.in

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Various subtituted 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) derivatives are synthesized *via* enyne metathesis and the Diels–Alder reaction.

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (Tic) is a phenylalanine analogue in which the dihedral angle χ is limited to a very small range because of its bicyclic nature.[1] In connection with the design of topographically constrained peptides Tic has been utilized in several instances as a replacement of phenylalanine or tyrosine.[2] Moreover, the tetrahydroisoquinoline unit is an important structural element in several important alkaloids and other medicinally useful products.[3] Availability of synthetic methods for the preparation of various Tic derivatives with varying degrees of steric/electronic and hydrophobic properties are useful in receptor mapping and also in designing meaningful QSAR studies.[4] In connection with our building block approach for the preparation of constrained amino acid derivatives[5] we sought a Diels–Alder strategy to prepare various unknown Tic derivatives **1**–**3**. Most of the known methods such as Bischler–Napieralski[6a] Picter–Spengler[6b] and among others[6c] for Tic preparation starts with the preformed benzene derivatives while our methodology involves generation of a benzene ring *via* the cycloaddition reaction as a key step. Consequently, the present methodology provides a unique opportunity to efficiently enhance the molecular complexity of inaccessible Tic derivatives. Here, we report our preliminary results for the preparation of various Tic derivatives using enyne metathesis and the Diels–Alder reaction as key steps.

Retrosynthetic routes for various Tic derivatives *via* Diels–Alder strategy as a key step are shown in Fig. 1. Pathways a and b in Fig. 1 lead to angularly substituted and pathway c to linearly substituted Tic derivatives. In exploring the synthesis of inner–outer ring dienes such as **4** and **5** containing a dehydropipicolinic acid moiety, we conceived a relatively less explored enyne metathesis reaction as a viable option. Conceptually, cycloiosomerization of a suitably functionalised 1,7-enyne building block is expected to deliver the 4,5-dimethylene pipicolinic acid derivative (*e.g.* **6**).

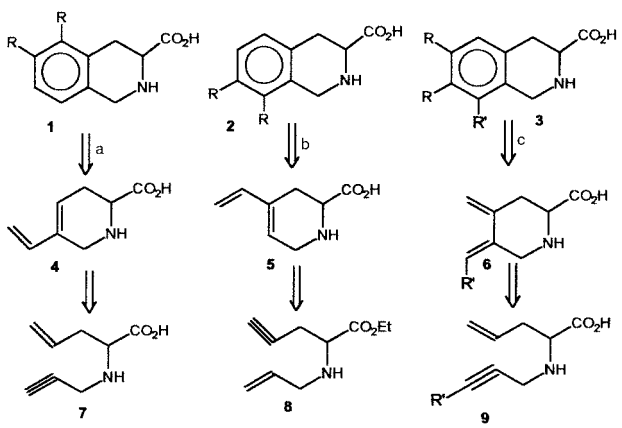
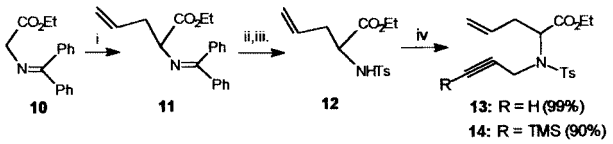


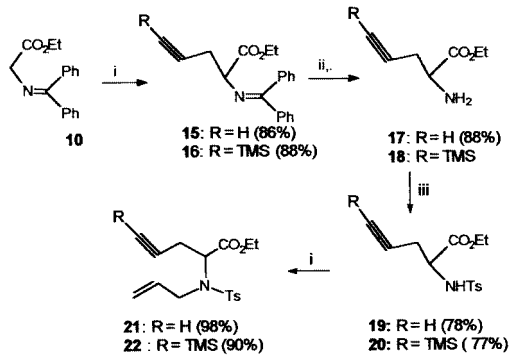
Fig. 1

Realization of the strategies shown in Fig. 1 require the preparation of key building blocks **7**, **8** and **9**. In this regard, ethyl *N*-(diphenylmethylene)glycinate **10**[7] was treated with allyl bromide in the presence of K_2CO_3 to give allylated product **11** (82%, Scheme 1). Hydrolysis of **11** with 1 M HCl in diethyl ether gave the amino ester which upon treatment with tosyl chloride in presence of triethylamine gave **12** in 78% yield [mp 43–44 °C, ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 143.1, 137.4, 131.5, 129.5, 127.4, 119.6, 61.4, 55.2, 37.7, 21.6, 14.0]. Reaction of **12** with propargyl bromide in the presence of K_2CO_3 gave **13** in quantitative yield. Under similar reaction conditions, enyne **14** was prepared in 90% yield.



Scheme 1 *Reagents and conditions*: i, allyl bromide, K_2CO_3, MeCN, 82%; ii, 1 M HCl, diethyl ether, 85%; iii, TsCl, Et_3N, CH_2Cl_2, 78%; iv, K_2CO_3, RC≡CCH_2Br, MeCN.

Towards the preparation of building blocks related to **8**, sequential reaction of ethyl *N*-(diphenylmethylene)glycinate **10** with propargyl bromide and 3-bromo-1-trimethylsilylprop-1-yne in the presence of K_2CO_3 in acetonitrile gave **15** (86%) and **16** (88%) respectively (Scheme 2). Hydrolysis of **15** with 1 M HCl in diethyl ether gave amino ester **17** (88%) which was protected as a tosyl derivative using tosyl chloride/triethylamine in dichloromethane at room temperature to give **19** (mp 48–49 °C). The structure of **19** is established by ^{1}H and ^{13}C NMR spectral data. During the hydrolysis of compound **16**, a minor amount of desilylated product was obtained which was separated (11%) after a protection sequence. The required compound **20** was obtained in 77% yield. Then allylation of compounds **19** and **20** in the presence of K_2CO_3 with allyl bromide gave **21** and **22** in 98 and 90% yields, respectively.



Scheme 2 *Reagents and conditions*: i, RC≡CCH_2Br, K_2CO_3, MeCN; ii, 1 M HCl, diethyl ether; iii, TsCl, Et_3N, CH_2Cl_2, 78%.

Having accomplished a high yielding synthesis of enyne building blocks **13** and **21**, we then focussed our attention towards the preparation of inner–outer ring dienes **24** and **25**.

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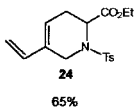
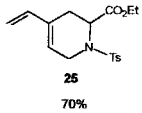
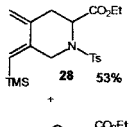
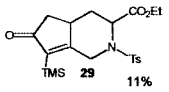
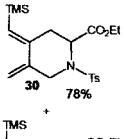
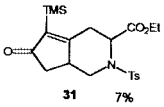
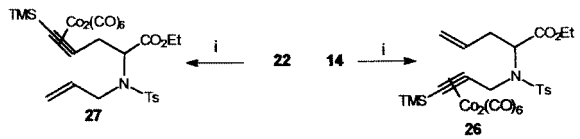
Table 1

Enyne	13	21	26	27
Reagents/ conditions	$(Cy_3P)Cl_2Ru{=}CHPh$/ 36 h	$(Cy_3P)Cl_2Ru{=}CHPh$/ 36 h	toluene/reflux	toluene/reflux
Diene	 24 65%	 25 70%	 28 53% +  29 11%	 30 78% +  31 7%

Thus, treatment of **13** with Grubb's catalyst[8] in refluxing toluene gave **24** in 65% isolated yield after column chromatography. Under similar reaction conditions diene **25** was prepared (70%) from enyne **21** (Table 1). Attempts to convert enynes **14** and **22** to the corresponding dienes by enyne metathesis conditions were not rewarding.

Next we turned our attention towards the preparation of silylated dienes **28** and **30**. Towards this goal, enyne **14** was treated with dicobalt octacarbonyl in diethyl ether to give compound **26** in 83% yield.[9] Similarly, enyne **27** was prepared in 84% yield (Scheme 3).



Scheme 3 *Reagents and conditions*: $Co_2(CO)_8$, diethyl ether, room temp.

Refluxing of enyne **26** in toluene followed by oxidative decomposition with *N*-methylmorpholine *N*-oxide yielded the 4,5-dimethylene pipicolinic acid derivative **28** in 53% yield along with a minor amount of Pauson–Khand product **29** (11%). The other diene **30** was obtained under similar reaction conditions in 78% yield along with the enone **31** (7%). It is worth mentioning that compound **31** is a useful precursor for tecomanine alkaloid.[10]

Having the dienes **24**, **25**, **28** and **30** in hand, we then examined their Diels–Alder chemistry with the readily available dienophiles (Table 2). The reaction of dienes **24** and **25** with different dienophiles and subsequent oxidation of Diels–Alder adducts with DDQ[11] gave angularly substituted Tic derivatives (**32**–**35**). Similarly, the Diels–Alder reaction of dienes **28** (or **30**) with dimethyl acetylenedicarboxylate (DMAD) and oxidation with DDQ gave desilylated product **36**.

In conclusion, for the first time we have demonstrated an exceptionally simple and versatile method for the synthesis of several Tic derivatives using enyne metathesis and the Diels–Alder reaction as key steps.

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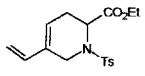
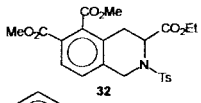
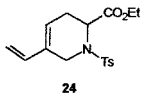
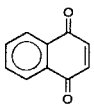
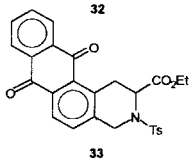
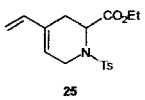
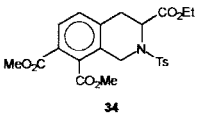
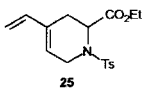
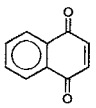
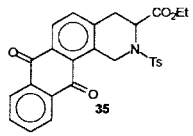
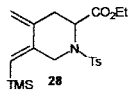
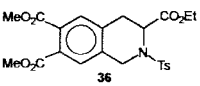
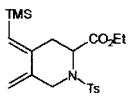
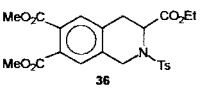
Table 2

Entry	Diene	Dienophile	DDQ product	Yield[a] (%)
1	 24		 32	93
2	 24		 33	52
3	 25		 34	85
4	 25		 35	45
5	 28		 36	69
6	 30		 36	65

[a]Yields refer to combined isolated yields for both the Diels–Alder reaction and DDQ oxidation.

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