Synthesis of 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid (Tic) Derivatives by Cycloaddition Approaches[‡]

Sambasivarao Kotha*[a] and Nampally Sreenivasachary[a]

Dedicated to Prof. C. Chattopadhyay on the occasion of his 60th birthday

Keywords: Amino acids / Combinatorial chemistry / Drug design / Metathesis / Peptides / Peptidomimetics

A new and general synthetic methodology for the preparation of functionalized 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives by a cycloaddition strategy is described. The synthesis of various enyne building blocks **12**, **13**, **21**, and **22** containing an α-amino acid moiety using Schiff base **8** as a glycine equivalent has been achieved under mild reaction conditions. These building blocks have been utilized in the synthesis of inner-outer ring dienes **23** and **24** and exocyclic dienes **26** and **29**, the key steps being an enyne metathesis reaction and cycloisomerization. Various topographically constrained Tic derivatives have been synthesized using dienes containing an α-amino acid moiety through Diels–Alder reactions. For the first time, [2+2+2] cyclotrimerization, as promoted by Wilkinson's and Vollhardt's catalysts, has been used for the synthesis of various highly functionalized Tic derivatives.

Introduction

Peptides are the natural messengers of the body and compounds of this type are expected to lead to very specific drugs with few side effects. However, unfavorable pharmacological properties such as metabolic instability and poor bioavailability of peptides often preclude their use as drugs.[1,2] Generally adopted methods for the development of peptide drugs involve the synthesis of restricted analogues that imitate the receptor-bound conformation of the endogenous ligands as closely as possible.[3] There are several other possibilities for the synthesis of conformationally restricted and metabolically stable peptides at the amino acid level.[4,5] One strategy involves the systematic replacement of individual amino acids with unusual amino acids bearing sterically demanding side chains. In this regard, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic, **1**) is an interesting constrained analogue of phenylalanine (Phe), in which a six-membered ring is formed by bridging with a methylene group *ortho* to the C atom of the phenyl ring and the peptide N atom (Figure 1). The insertion of Tic in the second chain position of several opioid peptides was found to have dramatic consequences with regard to their activity and selectivity.[6] Tic has also been use to replace Phe in farnesyl inhibitors, thereby generating selective and potent peptides.[7]

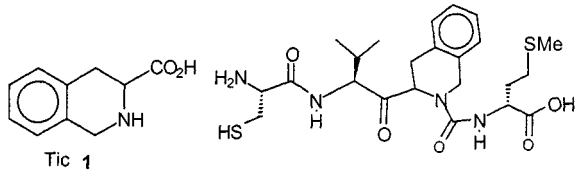


Figure 1. Farnesyl transferase inhibitor containing Tic

The availability of synthetic methods for the preparation of various Tic derivatives with varying degrees of steric/electronic and hydrophobic properties would be useful for receptor mapping and in designing meaningful QSAR studies.[8] However, known synthetic methods[9–11] for the preparation of Tic derivatives start with a preformed aryl ring synthon bearing electron-neutral or electron-rich substituents and provide very little opportunity for the introduction of additional functionalities.

Strategy

With regard to our interest in the development of new methodologies for cyclic α-amino acids (AAAs) by a building block approach,[12] we considered the possibility of utilizing a cycloaddition reaction as the key step. Whereas the known methods for Tic preparation start with preformed benzene derivatives, the present methodology involves generation of the benzenoid ring by a cycloaddition reaction. Consequently, the present methodology provides a unique opportunity for preparing otherwise inaccessible Tic derivatives by appropriate selection of the reacting partners. A

[‡] N. Sreenivasachary, Ph.D. Thesis, Indian Institute of Technology Bombay, **2000**. For a preliminary communications, see: S. Kotha, N. Sreenivasachary, *J. Chem. Soc., Chem. Commun.* **2000**, 503; S. Kotha, N. Sreenivasachary, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1413.

[a] Department of Chemistry, Indian Institute of Technology, Bombay,
Powai, Mumbai 400076, India
Fax: (internat.) + 91-22/572-3480
E-mail: srk@chem.iitb.ac.in

Supporting information for this article is available on the WWW under http://www.eurjoc.com or from the author.

  1434–193X/01/0917–3375 $ 17.50+.50/0

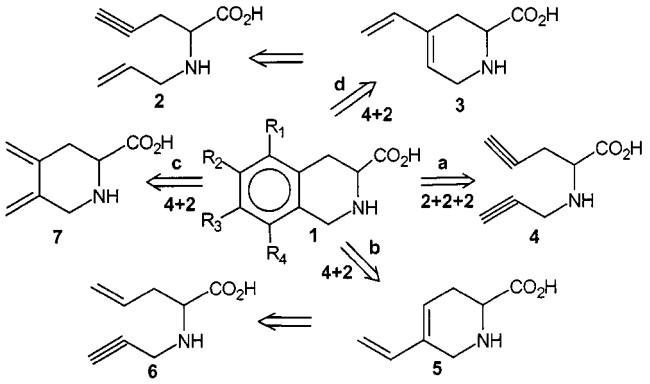


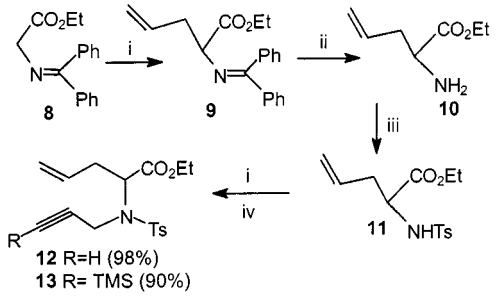
Figure 2. Retrosynthetic analysis for Tic derivatives

retrosynthetic analysis for Tic based on a cycloaddition strategy is shown in Figure 2.

Path **a** in Figure 2 involves a [2+2+2] cycloaddition reaction as the key step. This strategy involves co-trimerization of diyne **4** with a suitable monoyne to deliver the substituted Tic derivatives. Paths **b**–**d** are based on a [4+2] cycloaddition reaction as the key step. Pathways **b** and **d** require inner-outer ring dienes **3** and **5** containing an AAA moiety and lead to angularly substituted Tic derivatives. The requisite precursors may easily be prepared from enyne building blocks **2** and **6**. Path **c** requires exocyclic diene **7**, which can be prepared by cycloisomerization of enyne building blocks **2** and **6**. Diels–Alder reactions of **7** with suitable dienophiles followed by oxidation yield the linearly substituted Tic derivatives.

Results and Discussion

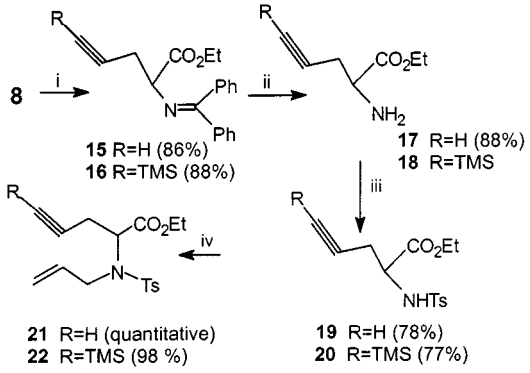
Initially, our attention was focused on the synthesis of enyne building blocks **2** and **6**. For this purpose, ethyl *N*-(diphenylmethylene)glycinate (**8**)[13] was chosen as a glycine equivalent. Treatment of the Schiff base **8** with allyl bromide in the presence of K_2CO_3 in refluxing acetonitrile gave the allylated product **9** in 82% yield (Scheme 1). Hydrolysis of **9** with 1 M HCl in diethyl ether gave amino ester **10** in 85% yield.



Scheme 1. Reagents: (i) allyl bromide, K_2CO_3, CH_3CN/reflux, 82%; (ii) 1 N HCl, diethyl ether, 85%; (iii) TsCl, Et_3N, CH_2Cl_2, 78%; (iv) 3-bromo-1-trimethylsilyl-1-propyne (**14**), K_2CO_3/CH_3CN

Protection of the amino group in **10** with *p*-toluenesulfonyl chloride in the presence of triethylamine in CH_2Cl_2 at room temp. gave the tosylated derivative **11** in 78% isolated yield (m.p. 43–44 °C). Reaction of **11** with propargyl bromide in the presence of K_2CO_3 gave the enyne building block **12** in quantitative yield. The enyne building block **13** was synthesized in 90% yield by treating **11** with 3-bromo-1-trimethylsilyl-1-propyne (**14**) under similar conditions (Scheme 1).

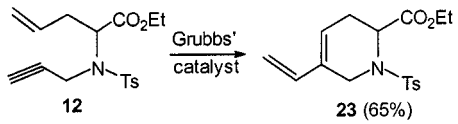
For the preparation of the enyne building block corresponding to **2**, compound **8** was treated with propargyl bromide in the presence of K_2CO_3 in acetonitrile to give **15** (Scheme 2). Hydrolysis of **15** with 1 M HCl in diethyl ether gave amino ester **17** (88%).[12g] Subsequent protection of **17** with *p*-toluenesulfonyl chloride in the presence of triethylamine gave compound **19** in 78% yield. Treatment of compound **19** with allyl bromide in the presence of K_2CO_3 gave the enyne building block **21** in quantitative yield.



Scheme 2. Reagents: (i) **14**, K_2CO_3/CH_3CN; (ii) 1 N HCl, diethyl ether; (iii) TsCl, Et_3N/CH_2Cl_2; (iv) allyl bromide, K_2CO_3/CH_3CN

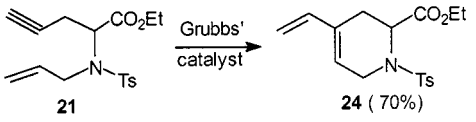
In order to prepare **22**, compound **8** was treated with bromo acetylene **14** in the presence of K_2CO_3 to give acetylene derivative **16** (88%; Scheme 2). During the hydrolysis of compound **16**, a minor amount of desilylated product **17** (11%) was formed, which was separated after the protection sequence. The required compound **20** was obtained in 77% yield after protection. Allylation of compound **20** using allyl bromide in the presence of K_2CO_3 gave **22** (Scheme 2).

Having accomplished a high-yielding synthesis of enyne building blocks **12**, **13**, **21**, and **22**, we turned our attention to the preparation of inner-outer ring dienes **3** and **5**. Thus, treatment of **12** with Grubbs' ruthenium catalyst $[Cl_2(PCy_3)_2Ru{=}CHPh]$[14] in refluxing toluene gave **23** in 65% isolated yield after column chromatography (Scheme 3).



Scheme 3

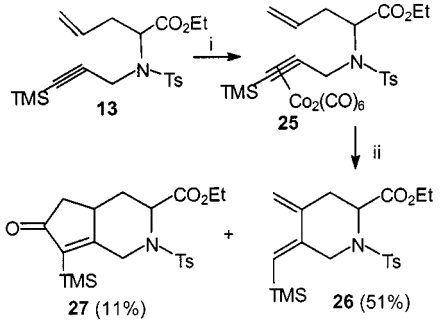
The structure of diene **23** was deduced from its spectroscopic data. Under similar reaction conditions, diene **24** was



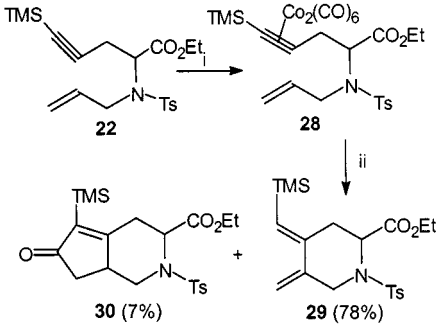
Scheme 4

prepared in 70% isolated yield from enyne **21** (Scheme 4) and its structure was also established by spectroscopic methods.

Despite the large number of literature reports concerning the synthesis of carbocycles, very few nitrogen-containing heterocycles have been prepared by isomerization methodologies. In this regard, Krafft and co-workers have reported the thermolysis of the hexacarbonyldicobalt complex of a 1,7-enyne to yield a monocyclic 1,3-diene.[15] Having prepared the dienes **23** and **24**, we turned our attention to the preparation of silylated exocyclic dienes. To this end, enyne **13** was treated with octacarbonyldicobalt in diethyl ether to give compound **25** (83%, Scheme 5).[16] Likewise, a cobalt complex of enyne **28** was prepared from enyne **22** in 85% yield (Scheme 6).



Scheme 5. (i) $Co_2(CO)_8$, diethyl ether, room temp., 83%; (ii) toluene, reflux, ΔT



Scheme 6. (i) $Co_2(CO)_8$, diethyl ether, room temp., 85%; (ii) toluene, reflux, 4-methylmorpholine *N*-oxide, $CHCl_3$

Refluxing a solution of enyne **25** in toluene followed by oxidative decomposition with 4-methylmorpholine *N*-oxide yielded the 4,5-dimethylenepipecolinic acid derivative **26** in 51% yield along with a minor amount of the Pauson−Khand product **27** (11%; Scheme 5).[17] The other diene **29** was obtained under similar conditions in 78% yield, accompanied by some bicyclic enone **30** (Scheme 6).

The 13-line ^{13}C NMR spectrum of **29** with diagnostic resonances at $\delta = 0.3$ (TMS) and $\delta = 142.3/150.0$ (*exo*-methylene carbon atoms) confirmed the structure of **29**. The structure of the Pauson−Khand product **30** was established by comparing the spectroscopic data with those of **27**. It is worth mentioning here that compound **30** represents a useful precursor for tecomanine-type alkaloids (Figure 3).[18]

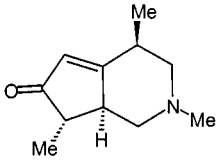


Figure 3. Tecomanine

Having prepared the dienes **23**, **24**, **26**, and **29**, their participation in the Diels−Alder (DA) reaction was examined with readily available dienophiles (Table 1). The reaction of diene **23** with dimethyl acetylenedicarboxylate (DMAD) gave the DA adduct along with the oxidized product (Scheme 7). In view of this, no attempt was made to isolate the DA product, and further oxidation of the DA adduct with DDQ was carried out to give the aromatized product **31**.

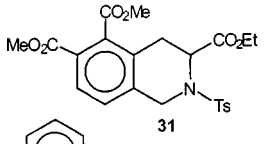
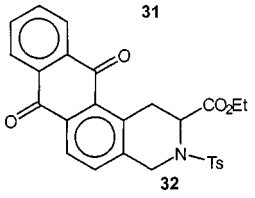
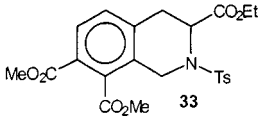
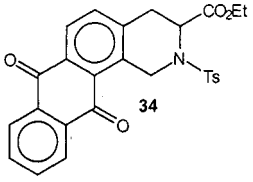
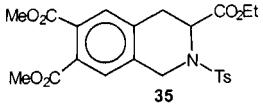
Similarly, other dienophiles such as naphthoquinone underwent [4+2] cycloaddition reactions and subsequent oxidation with DDQ to give the corresponding Tic derivatives. The Diels−Alder reaction of diene **24** with DMAD and naphthoquinone gave the [4+2] cycloaddition product. Subsequent oxidation of the DA adducts with DDQ gave various topographically oriented Tic derivatives. The reaction of exocyclic dienes **26** and **29** with DMAD followed by dehydrogenation in the presence of DDQ gave the desilylated product **35** (Table 1).

In continuation of our efforts towards the synthesis of Tic derivatives, a catalytic [2+2+2] cycloaddition reaction was also explored (Scheme 8). Recently, [2+2+2] cycloaddition reactions have been shown to offer one of the most efficient means of constructing various polycyclic ring systems. This reaction has been extensively studied using a variety of metal catalysts.[19−26]

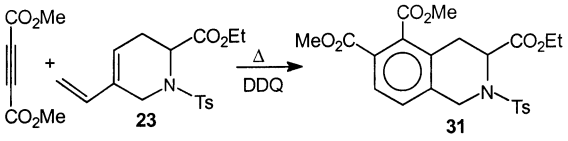
Due to the simple nature of the reaction conditions, Wilkinson's catalyst was chosen to effect the co-cyclotrimerization reaction. For the synthesis of the diyne building blocks related to **4** required for the trimerization leading to Tic derivatives, the reaction of **15** with propargyl bromide in the presence of K_2CO_3 and acetonitrile gave the diyne building block **36**. Along similar lines, the reaction of **15** with bromide **14** in the presence of K_2CO_3 in acetonitrile at room temperature gave **37** (98%; Scheme 9).

The feasibility of the [2+2+2] cyclotrimerization reaction with various acetylenic moieties using Wilkinson's catalyst (WC) was examined. Thus, the reaction of diyne **36** with 2-butyne-1,4-diol in refluxing ethanol in the presence of Wilkinson's catalyst gave the co-trimerized product **38** in 53% isolated yield (Scheme 10).

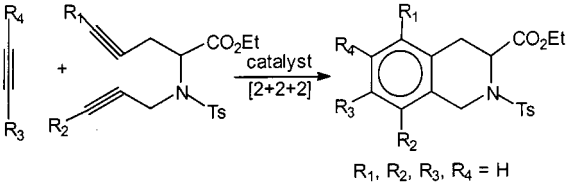
Table 1. Synthesis of Tic derivatives by a [4+2] cycloaddition strategy with dienes **23**, **24**, **26**, and **29**

S. No	Diene	Dienophile[a]	Product	Yield[b] (%)
1	23	a	 **31**	93
2	23	b	 **32**	52
3	24	a	 **33**	85
4	24	b	 **34**	45
5	26/29	a	 **35**	69/65

[a] a = DMAD, b = 1,4-naphthoquinone. – [b] Yields refer to combined isolated yields for both the Diels–Alder reaction and DDQ oxidation.

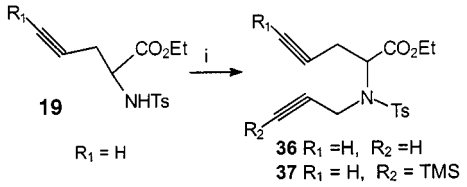


Scheme 7

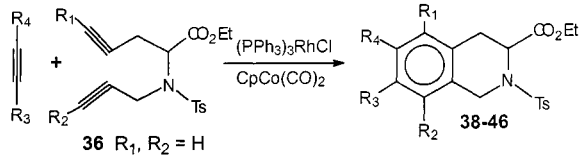


Scheme 8

In order to establish the generality and scope of this strategy, diyne **36** was treated with other monoynes in the presence of WC to give the co-trimerized products. The results are summarized in Scheme 10. Compounds **40**–**42** were obtained as 1:1 regioisomeric mixtures, as confirmed by ^1H and ^{13}C NMR spectroscopic data.



Scheme 9. Reagents: (i) **14** or propargyl bromide/K_2CO_3



			WC catalyst yields (%)	VC catalyst yields (%)
35	R_1, R_2 = H	R_3, R_4 = CO_2Me	–	19
38	R_1, R_2 = H	R_3, R_4 = CH_2OH	53	–
39	R_1, R_2 = H	R_3, R_4 = Ph	15	30
40[a]	R_1, R_2 = H	R_3 = Ph, R_4 = H	30	40
41[a]	R_1, R_2 = H	R_3 = CH_2OH, R_4 = H	60	–
42[a]	R_1, R_2 = H	R_3 = $(CH_2)_2OH$, R_4 = H	65	–
43	R_1, R_2 = H	R_3, R_4 = TMS	–	20
44	R_1 = H, R_2 = TMS	R_3, R_4 = CO_2Me	–	45
45	R_1 = H, R_2 = TMS	R_3, R_4 = Ph	–	42
46[a]	R_1 = H, R_2 = TMS	R_3 = H, R_4 = Ph	–	40

[a] Regioisomeric mixture.

Scheme 10

Later efforts were focused on the co-trimerization reactions of diyne **37**. Attempted reactions of diyne **37** with 2-butyne-1,4-diol and DMAD in the presence of WC were unsuccessful. Thus, co-trimerization of diyne **37** with various monoynes was explored using alternative catalysts. In this regard, Vollhardt's catalyst (VC), $CpCo(CO)_2$, was selected for study since it has proved to be useful when trimethylsilyl groups are present in either of the reacting partners. The major objective behind the selection of this catalyst was the introduction of a TMS group in the Tic derivatives, which, in turn, would allow us to exploit the excellent leaving group abilities of trialkylsilyl groups in electrophilic aromatic substitution reactions.[27] Trialkylsilyl groups are also known for having non-polar, hydrophobic properties appropriate for biological activity.[28] In this regard, many silicon-containing AAAs have been reported in the literature.[29] Peptides containing silicon residues in place of natural AAAs may exhibit enhanced biological activities, tissue absorbance properties, and proteolytic stabilities due to the hydrophobicity and large spatial requirements of the trialkylsilyl side chains.

High-dilution conditions and the use of excess monoyne proved to be essential for the success of this reaction. Thus, slow addition of the monoyne bis(trimethylsilyl)acetylene (BTMSA) containing the catalyst $CoCp(CO)_2$ to a refluxing solution of diyne **36** in BTMSA also containing the catalyst

under inert conditions gave the required product **43** (Scheme 10).

Similarly, the diyne building block **37** was co-trimerized with DMAD in the presence of the cobalt catalyst to give co-trimerized product **44** (Scheme 10). To assess the generality of the methodology, building blocks **36** and **37** were co-trimerized with various monoynes in the presence of the cobalt catalyst; the results are summarized in Scheme 10.

Conclusions

A new and general synthetic methodology has been developed for the synthesis of functionalized Tic derivatives based on [4+2] and [2+2+2] cycloaddition strategies. Using AAA-containing dienes such as **23**, **24**, **26**, and **29**, we have synthesized various topographically constrained Tic derivatives which are inaccessible by known methods. For the first time, [2+2+2] cyclotrimerizations promoted by Wilkinson's and Vollhardt's catalysts have been used for the synthesis of various highly funtionalized Tic derivatives. We have also demonstrated the utility of the enyne metathesis reaction in the preparation of heterocyclic dienes.

Experimental Section

General Remarks: A Razel A-99 syringe pump was used in all high-dilution reactions. Dry toluene and *n*-octane were obtained by distillation from sodium. *N*,*N*-Diisopropylamine and trimethylsilyl chloride were freshly distilled from CaH_2. *p*-Toluenesulfonyl chloride (TsCl) was purified prior to use by washing a solution in diethyl ether with 20% aq. NaOH and water, followed by crystallization from diethyl ether. Wilkinson's catalyst, 2-butyne-1,4-diol, phenylacetylene, and trimethylsilylacetylene were purchased from Aldrich Chemical Co. The catalyst $CpCo(CO)_2$ was purchased from Strem Chemicals Inc. 3-Butyn-1-ol and bis(trimethylsilyl)acetylene were obtained from Lancaster Synthesis.

Ethyl 2-[(4-Methylphenyl)sulfonyl]aminopent-4-enoate (11): To a solution of amino ester **10** (200 mg, 2.05 mmol) and triethylamine (630 mg, 6.2 mmol) in CH_2Cl_2 (15 mL), TsCl was added portionwise. The reaction mixture was stirred at room temp. for 6 h and then concentrated to dryness. The residue was taken up in ethyl acetate (100 mL) and the resulting solution was washed with 1 M HCl (10 mL), water, and brine, and dried with $MgSO_4$. Evaporation of the solvent left the crude product, which was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:20) to give **11** as a white solid (455 mg, 75%); m.p. 43−44 °C. − IR (neat): $\tilde{\nu}$ = 3278, 1737, 1650, 1599 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 6.1 Hz, 3 H), 2.42 (s, 3 H), 2.47 (m, 2 H), 3.95 (q, *J* = 6.3 Hz, 2 H), 5.04−5.10 (m, 2 H), 5.29 (m, 1 H), 5.59−5.70 (m, 1 H), 7.26 (d, *J* = 7.8 Hz, 2 H), 7.70 (d, *J* = 8.4 Hz, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 14.0, 21.5, 37.7, 55.2, 61.4, 119.5, 127.4, 129.5, 131.5, 137.4, 143.1, 170.7. − MS: *m*/*z* = 297 [M^+].

Ethyl 2-{[(4-Methylphenyl)sulfonyl](prop-2-ynyl)amino}pent-4-enoate (12): To a solution of the tosyl derivative **11** (75 mg, 0.25 mmol) in CH_3CN (10 mL) were added K_2CO_3 (105 mg, 0.75 mmol) and propargyl bromide (90 mg, 0.75 mmol). The resulting heterogeneous mixture was heated at 60 °C for 5 h. It was then filtered and concentrated. The residue was taken up in diethyl ether (100 mL) and the resulting solution was washed with water and brine and dried with $MgSO_4$. Evaporation of the solvent left the crude product, which was purified by column chromatography (silica gel; ethyl acetate/hexane, 1:20) to give **12** as a colorless liquid (83 mg, 98%). − IR (neat): $\tilde{\nu}$ = 3278, 2122, 1737 1650, 1598 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 6.9 Hz, 3 H), 2.15 (t, *J* = 2.4 Hz, 1 H), 2.39 (s, 3 H), 2.54−2.70 (m, 2 H), 3.96−4.02 (m, 2 H), 4.17 (t, *J* = 2.7 Hz, 2 H), 4.53 (t, *J* = 8.7 Hz, 1 H), 5.02−5.14 (m, 2 H), 5.68−5.74 (m, 1 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 13.8, 21.5, 34.0, 34.4, 59.1, 61.3, 72.6, 79.0, 118.5, 127.6, 129.3, 133.0, 136.8, 143.5, 170.2. − HRMS (EI): *m*/*z* for $C_{14}H_{18}NO_4S$ [M − $CH_2C{\equiv}CH$]: calcd. 295.0946; found 295.0833.

Ethyl 2-{[(4-Methylphenyl)sulfonyl](3-trimethylsilylprop-2-ynyl)amino}pent-4-enoate (13): To a solution of the tosyl derivative **11** (410 mg, 1.38 mmol) in CH_3CN (15 mL) were added 3-bromo-1-(trimethylsilyl)-1-propyne (**14**) (263 mg, 1.38 mmol) and K_2CO_3 (571 mg, 9.14 mmol). The resulting reaction mixture was heated at 65 °C for 5 h. It was then filtered and the filtrate was concentrated. The residue was taken up in diethyl ether (150 mL) and the resulting solution was washed with water and brine and dried with $MgSO_4$. Evaporation of the solvent left the crude product, which was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:20) to give **13** as a colorless liquid (506 mg, 90%). − IR (neat): $\tilde{\nu}$ = 3278, 2179, 1739, 1650, 1598 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.1 (s, 9 H), 1.08 (t, *J* = 7.5 Hz, 3 H), 2.33 (s, 3 H), 2.49−2.60 (m, 2 H), 3.92−3.99 (m, 2 H), 4.04 ($^1/_2$ ABq, *J* = 19.2 Hz, 1 H), 4.23 ($^1/_2$ ABq, *J* = 18.6 Hz, 1 H), 4.45 (dd, *J* = 6.6, 8.7 Hz, 1 H), 4.93−5.07 (m, 2 H), 5.60−5.69 (m, 1 H), 7.20 (d, *J* = 7.8 Hz, 2 H), 7.72 (d, *J* = 8.1 Hz, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 0.4, 14.8, 22.4, 35.2, 35.9, 60.2, 62.1, 90.3, 101.4, 119.1, 128.6, 130.1, 134.1, 138.1, 144.2, 171.0. − HRMS (EI): *m*/*z* for $C_{19}H_{26}NO_4SSi$ [M − CH_3]: calcd. 392.13518; found 392.13357.

Ethyl 2-{[(4-Methylphenyl)sulfonyl]amino}pent-4-ynoate (19): To a solution of amino ester **17** (150 mg, 1.06 mmol) and triethylamine (203 mg, 2.0 mmol) in CH_2Cl_2 (10 mL), TsCl was added portionwise. The reaction mixture was stirred at room temp. for 6 h and then concentrated to dryness. The residue was taken up in ethyl acetate (100 mL) and the resulting solution was washed with 1 M HCl, water, and brine, and dried with $MgSO_4$. Evaporation of the solvent left the crude product, which was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:20) to give **19** as a white crystalline solid (240 mg, 78%); m.p. 48−49 °C. − IR (neat): $\tilde{\nu}$ = 3283, 2123, 1738, 1598 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 6.9 Hz, 3 H), 1.95 (t, *J* = 2.7 Hz, 1 H), 2.41 (s, 3 H), 2.61−2.71 (m, 2 H), 3.99−4.12 (m, 3 H), 5.40 (d, *J* = 6.0 Hz, 1 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 7.77 (d, *J* = 8.1 Hz, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 14.0, 21.4, 24.0, 54.0, 62.0, 72.1, 77.6, 127.2, 129.4, 137.2, 143.2, 169.3. − MS: *m*/*z* = 295 [M^+].

Ethyl 2-{[(4-Methylphenyl)sulfonyl](prop-2-enyl)amino}pent-4-ynoate (21): To a solution of the tosyl derivative **19** (100 mg, 0.33 mmol) in CH_3CN (10 mL) were added allyl bromide (100 mg, 1.0 mmol) and K_2CO_3 (150 mg, 1.0 mmol). The resulting reaction mixture was stirred for 12 h at room temp. It was then filtered and concentrated. The residue was taken up in diethyl ether (100 mL) and the resulting solution was washed with water and brine and dried with $MgSO_4$. Evaporation of the solvent left the crude product, which was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:20) to give **21** as a colorless liquid (112 mg,

quantitative yield). − IR (neat): $\tilde{\nu}$ = 3284, 2123, 1739, 1642, 1598 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.2 Hz, 3 H), 1.96 (t, *J* = 2.4 Hz, 1 H), 2.39 (s, 3 H), 2.67 (dd, $^1/_2$ ABq, *J* = 3.0, 8.7, 17.1 Hz, 1 H), 2.84 (dd, $^1/_2$ ABq, *J* = 3.0, 6.4, 16.9 Hz, 1 H), 3.86 (dq, *J* = 9.9, 16.2 Hz, 2 H), 4.04 (q, *J* = 7.2 Hz, 2 H), 4.67 (dd, *J* = 6.0, 9.0 Hz, 1 H), 5.06−5.20 (m, 1 H), 5.73−5.84 (m, 2 H), 7.25 (d, *J* = 8.1 Hz, 2 H), 7.73 (d, *J* = 8.4 Hz, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 14.0, 20.9, 21.4, 48.7, 58.4, 61.6, 71.3, 79.4, 118.1, 127.6, 129.3, 134.4, 137.1, 143.4, 169.3. − HRMS (EI): *m*/*z* for $C_{14}H_{18}NO_4S$ [M − $CH_2C{\equiv}CH$]: calcd. 296.0956; found 295.0956.

Ethyl 2-{[(4-Methylphenyl)sulfonyl](5-trimethylsilylprop-2-enyl)-amino}pent-4-ynoate (22): To a solution of the tosyl derivative **20** (70 mg, 0.19 mmol) in CH_3CN (5 mL) were added allyl bromide (46 mg, 0.38 mmol) and K_2CO_3 (52 mg, 0.38 mmol). The resulting heterogeneous reaction mixture was stirred at room temp. for 6 h. It was then filtered and concentrated. The residue was taken up in diethyl ether (100 mL) and the resulting solution was washed with water and brine and dried with $MgSO_4$. Evaporation of the solvent left the crude product, which was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:20) to give **22** as a colorless liquid (75 mg, 98%). − IR (neat): $\tilde{\nu}$ = 2179, 1739, 1598 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.01 (s, 9 H), 1.08 (t, *J* = 7.2 Hz, 3 H), 2.30 (s, 3 H), 2.74 (dq, *J* = 6.3, 17.4 Hz, 2 H), 3.83 (dq, *J* = 6.6, 16.5 Hz, 2 H), 3.96 (q, *J* = 7.2 Hz, 2 H), 4.52 (dd, *J* = 8.4, 6.0 Hz, 1 H), 4.97−5.13 (m, 2 H), 5.67−5.73 (m, 1 H), 7.16 (d, *J* = 7.8 Hz, 2 H), 7.65 (d, *J* = 8.4 Hz, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 0.2, 13.9, 21.4, 22.4, 49.1, 58.6, 61.5, 88.0, 101.8, 117.9, 127.5, 129.3, 134.7, 137.3, 143.3, 169.4. − HRMS (EI): *m*/*z* for $C_{19}H_{26}NO_4SSi$ [M − CH_3]: calcd. 392.1351; found 392.1344.

Preparation of Cobalt Complex 25: To a solution of $Co_2(CO)_8$ (212 mg, 0.62 mmol) in dry diethyl ether (35 mL) was added the enyne building block **13** (252 mg, 0.62 mmol). The brown solution thus obtained was stirred at room temp. for 10 h under argon. A suspension was produced, which was filtered through a sintered glass crucible. The filtrate was concentrated and the crude product was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:20) to give **25** as a sticky solid (357 mg, 83%). − IR (neat): $\tilde{\nu}$ = 2088, 2051, 2032, 1737 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.37 (s, 9 H), 1.10 (t, *J* = 7.5 Hz, 3 H), 2.42 (s, 3 H), 2.65 (t, *J* = 7.2 Hz, 2 H), 3.71−3.93 (m, 2 H), 4.44 (t, *J* = 7.8 Hz, 1 H), 4.83 (s, 2 H), 5.07−5.15 (m, 1 H), 5.68−5.82 (m, 2 H), 7.29 (d, *J* = 8.1 Hz, 2 H), 7.71 (d, *J* = 8.1 Hz, 2 H).

Preparation of Cobalt Complex 28: To a stirred solution of $Co_2(CO)_8$ (168 mg, 0.49 mmol) in dry diethyl ether (25 mL) was added the enyne building block **22** (200 mg, 0.49 mmol). The brown solution thus obtained was stirred at room temp. for 12 h under argon. A suspension was produced, which was filtered through a sintered glass crucible. The filtrate was concentrated and the residue was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:20) to give **28** (288 mg, 85%) as a dark-brown gummy solid. − IR (neat): $\tilde{\nu}$ = 2088, 2051, 2034, 1741 cm^{-1}.

Ethyl *N*-[(4-Methylphenyl)sulfonyl)-5-vinyl-1,2,3,6-tetrahydropyridine-2-carboxylate (23): To a solution of the enyne building block **12** (100 mg, 0.29 mmol) in toluene was added Grubbs' catalyst [$Cl_2(PCy_3)_2Ru{=}CHPh$] (20 mol%) and the reaction mixture was refluxed under argon for 36 h. The solvents were then evaporated to leave the crude product, which was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:10) to give the diene **23** as a colorless liquid (65 mg, 65%). − IR (neat): $\tilde{\nu}$ = 1736 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 6.8 Hz, 3 H), 2.42 (s, 3 H), 2.64 (m, 2 H), 3.83−4.06 (m, 3 H), 4.25 ($^1/_2$ ABq, *J* = 15.2 Hz, 1 H), 4.86 (t, *J* = 6.3 Hz, 1 H), 5.02 (dd *J* = 6.6, 15.6 Hz, 2 H), 5.71 (s, 1 H), 6.23 (dd, *J* = 11.0, 18.4 Hz, 1 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 7.70 (d, *J* = 8.0 Hz, 2 H). − HRMS (EI): *m*/*z* for $C_{14}H_{18}NO_4S$ [M − C_3H_3N]: calcd. 278.0850; found 278.0854

Ethyl *N*-[(4-Methylphenyl)sulfonyl]-4-vinyl-1,2,3,6-tetrahydropyridine-2-carboxylate (24): To a solution of the enyne building block **21** (210 mg, 0.62 mmol) in toluene was added Grubbs' catalyst [$Cl_2(PCy_3)_2Ru{=}CHPh$] (20 mol%) and the reaction mixture was refluxed under argon for 36 h. It was then concentrated and the crude product was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:10) to give the diene **24** as a colorless liquid (150 mg, 70%). − IR (neat): $\tilde{\nu}$ = 1736, 1645 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.9 (t, *J* = 6.9 Hz, 3 H), 2.3 (s, 3 H), 2.4 ($^1/_2$ ABq, *J* = 17.0 Hz, 1 H), 2.7 ($^1/_2$ ABq, *J* = 17.1 Hz, 1 H), 3.7−3.9 (m, 3 H), 4.1 ($^1/_2$ ABq, *J* = 18.0 Hz, 1 H), 4.88 (d, *J* = 5.7 Hz, 1 H), 4.9−5.0 (m, 2 H), 5.5 (s, 1 H), 6.23 (dd, *J* = 10.8, 17.4 Hz, 1 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 7.62 (d, *J* = 8.1 Hz, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 13.8, 21.4, 26.8, 42.2, 52.7, 61.2, 112.4, 123.1, 127.2, 129.4, 131.8, 136.2, 137.4, 143.3, 170.0 (C=O). − HRMS (EI): *m*/*z* for $C_{14}H_{18}NO_4S$ [M − C_3H_3N]: calcd. 278.0850; found 278.0854.

Preparation of Compounds 26 and 27: A solution of dicobalt complex **25** (275 mg, 0.39 mmol) in toluene (95 mL) was added dropwise to refluxing toluene (50 mL) under argon over a period of 25 min. The resulting suspension was refluxed for a further 30 min and was then allowed to cool to ambient temperature, whereupon a solution of 4-methylmorpholine *N*-oxide (140 mg, 1.1 mmol) in $CHCl_3$ (10 mL) was added. The reaction mixture was filtered, the filtrate was concentrated, and the residue obtained was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:20) to give diene **26** (85 mg, 51%). − IR (neat): $\tilde{\nu}$ = 1737 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 0.02 (s, 9 H), 1.16 (t, *J* = 7.2 Hz, 3 H), 2.40 (s, 3 H), 2.46 (d, $^1/_2$ ABq, *J* = 6.6, 9.0 Hz, 1 H), 2.68 ($^1/_2$ ABq, *J* = 2.4, 13.5 Hz, 1 H), 3.96−4.10 (m, 3 H), 4.24 ($^1/_2$ ABq, *J* = 14.0 Hz, 1 H), 4.81 (dd, *J* = 3.3, 6.6 Hz, 1 H), 4.85 (d, *J* = 22.0 Hz, 2 H), 5.36 (s, 1 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 7.66 (d, *J* = 8.1 Hz, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 0.24, 14.1, 21.6, 37.0, 53.4, 56.5, 61.2, 114.5, 127.4, 127.5, 129.5, 137.2, 142.2, 143.2, 149.7, 169.6. − HRMS (EI): *m*/*z* for $C_{19}H_{26}NO_4S$ [M − CH_3]: calcd. 392.1351; found 392.1348. − Further elution of the column with ethyl acetate/hexane (1:10) gave the Pauson−Khand product **27** as a crystalline material (20 mg, 11%); m.p. 110−111 °C. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.22 (s, 9 H), 1.21 (t, *J* = 7.5 Hz, 3 H), 1.54−1.65 (m, 1 H), 1.92 (dd, *J* = 3.3, 18.3 Hz, 1 H), 2.42 (s, 3 H), 2.47−2.69 (m, 2 H), 2.69−2.73 (m, 1 H), 4.02−4.16 (m, 3 H), 4.86−4.93 (m, 2 H), 7.29 (d, *J* = 8.1 Hz, 2 H), 7.67 (d, *J* = 8.4 Hz, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 0.7, 14.1, 21.5, 34.7, 37.5, 41.4, 44.1, 54.6, 61.5, 127.3, 129.6, 136.6, 139.8, 143.5, 170.0, 177.6, 210.5. − HRMS (EI): *m*/*z* for $C_{20}H_{26}NO_4SSi$ [M − CH_3]: calcd. 420.13009; found 420.1304.

Preparation of Compounds 29 and 30: A solution of the hexacarbonyldicobalt complex of enyne **28** (250 mg, 0.36 mmol) in toluene (85 mL) was added dropwise to refluxing toluene (45 mL) under argon over a period of 25 min. The resulting suspension was refluxed for a further 30 min and was then allowed to cool to ambient temperature, whereupon a solution of 4-methylmorpholine *N*-oxide (140 mg, 1.1 mmol) in $CHCl_3$ (10 mL) was added. The reaction mixture was filtered, the filtrate was concentrated, and the residue obtained was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:20) to give the diene **29** as a viscous liquid

(115 mg, 78%). − IR (neat): $\tilde{\nu}$ = 1742 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 9 H), 1.11 (t, *J* = 6.9 Hz, 3 H), 2.40 (s, 3 H), 2.64 (d, *J* = 3.6 Hz, 2 H), 3.93−3.99 (m, 3 H), 4.28 ($^1/_2$ ABq, *J* = 5.4 Hz, 1 H), 4.79 (t, *J* = 3.9 Hz, 1 H), 4.97 (s, 2 H), 5.30 (s, 1 H), 7.25 (d, *J* = 7.8 Hz, 2 H), 7.65 (d, *J* = 8.1 Hz, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 0.3, 14.2, 21.5, 42.1, 49.6, 56.7, 61.0, 113.2, 127.1, 129.1, 129.4, 136.8, 142.3, 143.1, 150.0, 169.5. − HRMS (EI): *m*/*z* for $C_{19}H_{26}NO_4S$ [M − CH_3]: calcd. 392.1351; found 392.1347. − Further elution of the column with ethyl acetate/hexane (1:10) gave the Pauson−Khand product **30** as a gummy solid (10 mg, 7%). − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.17 (s, 9 H), 1.13 (t, *J* = 6.9 Hz, 3 H), 1.84 (d, *J* = 18.6 Hz, 2 H), 2.46 (s, 3 H), 2.69−2.76 (m, 1 H), 2.89−2.93 (m, 2 H), 3.44 ($^1/_2$ ABq, *J* = 13.8 Hz, 1 H), 3.85−4.07 (m, 2 H), 4.13 ($^1/_2$ ABq, *J* = 6.9 Hz), 5.02 (d, *J* = 3.9 Hz, 1 H), 7.29 (d, *J* = 8.1 Hz, 2 H), 7.77 (d, *J* = 8.1 Hz, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 0.12, 14.7, 22.2, 33.5, 39.4, 42.2, 49.5, 56.2, 62.2, 127.9, 130.2, 137.5, 141.8, 144.2, 169.6, 181.0, 210.9. − HRMS (EI): *m*/*z* for $C_{20}H_{26}NO_4SSi$ [M − CH_3]: calcd. 420.13009; found 420.1304.

Preparation of Compound 31: A solution of diene **23** (45 mg, 0.134 mmol), DMAD (32 mg, 0.099 mmol), and a catalytic amount of hydroquinone in dry toluene (3.5 mL) was placed in a thick-walled tube. The tube was then sealed and the reaction mixture was refluxed at 160 °C for 3 d. After opening the tube, the contents were concentrated and the residue was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:4) to give the Diels−Alder adduct as a colorless liquid (43 mg, 96%). Subsequently, a mixture of the DA adduct (25 mg, 0.052 mmol) and DDQ (11.8 mg, 0.082 mmol) in toluene (3.5 mL) was refluxed for 48 h. This mixture was then concentrated and the residue obtained was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:4) to give the aromatized product **31** as a viscous solid (24 mg, 97%). − IR (neat): $\tilde{\nu}$ = 1736 cm^{-1}. − UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) = 244 (34.01 × 10^3). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.2 Hz, 3 H), 2.41 (s, 3 H), 3.23 (d, *J* = 3.6 Hz, 2 H), 3.88 (s, 6 H), 3.80−3.98 (m, 2 H), 4.52 ($^1/_2$ ABq, *J* = 16.5 Hz, 1 H), 4.79 ($^1/_2$ ABq, *J* = 16.2 Hz, 1 H), 5.05 (dd, *J* = 3.6, 5.1 Hz, 1 H), 7.29 (d, *J* = 8.1 Hz, 2 H), 7.44 (d, *J* = 7.5 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H). − HRMS (EI): *m*/*z* for $C_{21}H_{20}NO_8S$ [M − CH_2CH_3]: calcd. 446.1180; found 446.10749.

Preparation of Compound 32: A solution of diene **23** (50 mg, 0.149 mmol), 1,4-naphthoquinone (60 mg, 0.37 mmol), and a catalytic amount of hydroquinone in dry toluene (3.5 mL) was placed in a thick-walled glass tube. The tube was then sealed and the reaction mixture was refluxed at 160 °C for 3.5 d. After opening the tube, the contents were concentrated and the residue was chromatographed on a silica gel column eluting with ethyl acetate/hexane (1:4) to give the DA adduct as a colorless liquid (56 mg, 77%). Subsequently, a mixture of the DA adduct (36 mg, 0.073 mmol) and DDQ (36 mg, 0.15 mmol) in toluene (3.5 mL) was refluxed for 72 h. The reaction mixture was then concentrated and the residue obtained was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:4) to give the aromatized product **32** as a yellow sticky material (24 mg, 67%). − IR (neat): $\tilde{\nu}$ = 1736 cm^{-1}. − UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) = 255 (46.030 × 10^3), 334 (7.80 × 10^3). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.2 Hz, 3 H), 2.40 (s, 3 H), 3.64 (dd, *J* = 6.9, 8.4 Hz, 1 H), 3.85−3.95 (m, 2 H), 4.17 ($^1/_2$ AXq, *J* = 18.3 Hz, 1 H), 4.70 ($^1/_2$ ABq, *J* = 16.2 Hz, 1 H), 4.83 ($^1/_2$ ABq, *J* = 15.9 Hz, 1 H), 5.06 (dd, *J* = 1.8, 2.1, 7.2 Hz, 1 H), 7.77 (d, *J* = 8.1 Hz, 2 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 7.74−7.82 (m, 4 H), 8.23 (d, *J* = 6.0 Hz, 3 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 13.9, 21.6, 22.7, 31.2, 45.0, 53.0, 61.3, 126.1, 126.7, 127.3, 129.6, 131.6, 132.6, 133.7, 133.9, 134.2, 134.4, 134.7, 135.9, 139.6, 143.6, 170.0, 182.7, 184.9. − HRMS (EI): *m*/*z* for $C_{27}H_{23}NO_6S$: calcd. 489.1230; found 489.1246.

Preparation of Compound 33: A solution of diene **24** (45 mg, 0.13 mmol), DMAD (38 mg, 0.26 mmol), and a catalytic amount of hydroquinone in dry toluene (3.5 mL) was placed in a thick-walled glass tube. The tube was then sealed and the reaction mixture was refluxed at 160 °C for 3 d. After opening the tube, the contents were concentrated and the residue was chromatographed on a silica gel column eluting with ethyl acetate/hexane (1:4) to give the DA adduct (60 mg, 95%) as a colorless liquid. Subsequently, a mixture of the DA adduct (58 mg, 0.121 mmol) and DDQ (37 mg, 0.145 mmol) in toluene (3.5 mL) was refluxed for 48 h. The reaction mixture was then concentrated and the residue obtained was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:4) to give the aromatized product **33** as a gummy material (50 mg, 87%). − IR (neat): $\tilde{\nu}$ = 1736 cm^{-1}. − UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) = 246.3 (24.035 × 10^3). − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.2 Hz, 3 H), 2.40 (s, 3 H), 3.22 (d, *J* = 6.0 Hz, 2 H), 3.81−3.98 (m, 2 H), 3.92 (s, 3 H), 3.94 (s, 3 H), 4.39 ($^1/_2$ ABq, *J* = 16.2 Hz, 1 H), 4.74 ($^1/_2$ ABq, *J* = 16.2 Hz, 1 H), 4.97 (dd, *J* = 3.3, 6.0 Hz, 1 H), 7.19 (d, *J* = 8.1 Hz, 1 H), 7.27 (d, *J* = 8.1 Hz, 2 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 7.75 (d, *J* = 8.1 Hz, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 13.8, 21.5, 32.1, 42.1, 52.4, 52.7, 53.1, 61.4, 126.8, 127.3, 128.1, 129.5, 129.6, 129.9, 133.1, 136.0, 136.5, 143.5, 165.6, 168.1, 169.5. − HRMS (EI): *m*/*z* for $C_{21}H_{20}NO_8S$: calcd. 446.1129; found 446.1074.

Preparation of Compound 34: A solution of diene **24** (52 mg, 0.155 mmol), naphthoquinone (48 mg, 0.31 mmol), and a catalytic amount of hydroquinone in dry toluene (3.5 mL) was placed in a thick-walled glass tube. The tube was then sealed and the reaction mixture was refluxed at 160 °C for 3.5 d. After opening the tube, the contents were concentrated and the residue was chromatographed on a silica gel column eluting with ethyl acetate/hexane (1:4) to give the DA adduct (53 mg, 70%) as a colorless liquid. Subsequently, a mixture of the DA adduct (32 mg, 0.065 mmol) and DDQ (14.7 mg, 0.065 mmol) in toluene (3.5 mL) was refluxed for 48 h. The reaction mixture was then concentrated and the residue obtained was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:4) to give **34** as a yellow sticky material (20 mg, 64%). − IR (neat): $\tilde{\nu}$ = 1736 cm^{-1}. − UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) = 258 (45.029 × 10^3), 335 (7.64 × 10^3). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.8 Hz, 3 H), 2.39 (s, 3 H), 3.31−3.34 (m, 2 H), 3.84−3.97 (m, 2 H), 4.85 ($^1/_2$ ABq, *J* = 18.9 Hz, 1 H), 5.10 (dd, *J* = 2.7, 6.3 Hz, 1 H), 5.61 ($^1/_2$ ABq, *J* = 18.6 Hz, 1 H), 7.27 (d, *J* = 9.0 Hz, 2 H), 7.54 (d, *J* = 8.1 Hz, 2 H), 7.72−7.76 (m, 2 H), 7.79 (d, *J* = 8.4 Hz, 2 H), 8.19−8.24 (m, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 13.8, 21.5, 33.1, 44.8, 52.7, 61.5, 126.2, 126.7, 127.3, 127.5, 129.5, 129.7, 132.3, 133.6, 133.8, 134.3, 134.4, 134.6, 135.2, 136.0, 139.1, 143.5, 169.7, 182.9, 184.8. − HRMS (EI): *m*/*z* for $C_{27}H_{23}NO_6S$: calcd. 489.1238; found 489.12461.

Preparation of Compound 35: A solution of diene **26** (26 mg, 0.063 mmol), DMAD (18 mg, 0.127 mmol), and a catalytic amount of hydroquinone in dry toluene (3.5 mL) was placed in a thick-walled glass tube. The tube was then sealed and the reaction mixture was refluxed at 150 °C for 48 h. After opening the tube, the contents were concentrated and the residue was chromatographed on a silica gel column eluting with ethyl acetate/hexane (1:4) to give the DA adduct (26 mg, 76%) as a colorless liquid. Subsequently, a mixture of the DA adduct (25 mg, 0.045 mmol) and DDQ (10.3 mg, 0.082 mmol) in toluene (3.5 mL) was refluxed for 48 h.

The reaction mixture was then concentrated and the residue obtained was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:4) to give the desilylated aromatized product **35** as a viscous liquid (19 mg, 90%). − IR (neat): $\tilde{\nu}$ = 1736 cm^{-1}. − UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) = 245 (10.766 × 10^3). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 6.9 Hz, 3 H), 2.41 (s, 3 H), 3.23 (d, *J* = 3.3 Hz, 2 H), 3.81−3.98 (m, 2 H), 3.88 (s, 6 H), 4.52 ($^1/_2$ ABq, *J* = 16.2 Hz, 1 H), 4.72 ($^1/_2$ ABq, *J* = 15.9 Hz, 1 H), 5.05 (dd, *J* = 3.2, 5.3 Hz, 1 H), 7.28 (d, *J* = 8.1 Hz, 2 H), 7.44 (d, *J* = 7.2 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 14.0, 21.6, 31.9, 44.1, 52.3, 53.0, 61.4, 129.1, 129.5, 129.6, 130.5, 130.6, 134.3, 134.9, 136.2, 143.4, 167.0, 169.2, 169.3. − HRMS (EI): *m/z* for $C_{21}H_{20}NO_8S$ [M − C_2H_5]: calcd. 446.1074; found 446.1148.

Ethyl 2-{[(4-Methylphenyl)sulfonyl](prop-2-ynyl)amino}pent-4-ynoate (36): To a solution of the tosyl derivative **19** (250 mg, 0.84 mmol) in CH_3CN (15 mL) were added propargyl bromide (150 mg, 1.27 mmol) and K_2CO_3 (350 mg, 2.5 mmol). The resulting heterogeneous reaction mixture was heated at 60 °C for 2 h. It was then filtered and concentrated. The residue was taken up in diethyl ether (100 mL) and the resulting solution was washed with water and brine and dried with $MgSO_4$. Evaporation of the solvent left the crude product, which was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:19) to give **36** as a white crystalline solid (231 mg, quantitative); m.p. 59−60 °C. − IR (neat): $\tilde{\nu}$ = 3283, 2123, 1738 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 6.9 Hz, 3 H), 1.88 (t, *J* = 2.7 Hz, 1 H), 2.06 (t, *J* = 2.4 Hz, 1 H), 2.30 (s, 3 H), 2.67 (d, $^1/_2$ ABq, *J* = 2.7, 7.8, 9.9 Hz, 1 H), 2.80 (d, $^1/_2$ ABq, *J* = 3.9, 8.7, 9.9 Hz, 1 H), 3.93−4.04 (m, 2 H), 4.09 (d, *J* = 7.8 Hz, 2 H), 4.63 (t, *J* = 7.8 Hz, 1 H), 7.16 (d, *J* = 9.6 Hz, 2 H), 7.68 (d, *J* = 8.4, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 13.8, 20.7, 21.4, 34.3, 58.0, 61.7, 71.5, 73.0, 78.3, 78.9, 127.7, 129.3, 136.7, 143.7, 169.0. − MS: *m/z* = 333 [M^+].

Ethyl 2-{[(4-Methylphenyl)sulfonyl](3-trimethylsilylprop-2-ynyl)-amino}pent-4-ynoate (37): To a solution of the tosyl derivative **19** (150 mg, 0.5 mmol) in CH_3CN (10 mL) were added 3-bromo-1-trimethylsilyl-1-propyne (115 mg, 0.6 mmol) and K_2CO_3 (200 mg, 1.5 mmol). The resulting heterogeneous mixture was heated at 60 °C for 3 h. It was then concentrated, the residue was taken up in diethyl ether (100 mL), the resulting solution was washed with water and brine, and dried with $MgSO_4$. Evaporation of the solvent left the crude product, which was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:30) to give **37** as a colorless liquid (198 mg, 98%). − IR (neat): $\tilde{\nu}$ = 3283, 2179, 1738 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 9 H), 1.19 (t, *J* = 7.2 Hz, 3 H), 1.95 (t, *J* = 2.7 Hz, 1 H), 2.42 (s, 3 H), 2.75 ($^1/_2$ ABq, *J* = 2.7, 8.1, 17.1 Hz, 1 H), 2.93 ($^1/_2$ ABq, *J* = 2.7, 6.6, 17.4 Hz, 1 H), 4.05−4.17 (m, 2 H), 4.21 ($^1/_2$ ABq, *J* = 17.8 Hz, 1 H), 4.27 ($^1/_2$ ABq, *J* = 18.6 Hz, 1 H), 4.75 (t, *J* = 6.9 Hz, 1 H), 7.27 (d, *J* = 7.8 Hz, 2 H), 7.83 (d, *J* = 8.4 Hz, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 0.03, 14.3, 21.1, 21.9, 35.8, 58.7, 62.1, 71.7, 79.7, 99.3, 100.2, 128.3, 129.7, 137.6, 143.9, 169.4. − HRMS (EI): *m/z* for $C_{19}H_{26}NO_4SSi$ [M − CH_3]: calcd. 392.13518; found 392.1335.

Synthesis of 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid Derivatives by Co-trimerization Reactions

General Procedure for [2+2+2] Cycloaddition Reactions Using Wilkinson's Catalyst: A solution of the diyne building block (1 mmol) and the monoyne (5−8 mmol) in absolute ethanol (20 mL) was degassed by bubbling argon through it for 30 min. Wilkinson's catalyst (2−3 mol%) was then added and the resulting clear red solution was refluxed under argon until all the diyne had been consumed (TLC monitoring). The solvent was then evaporated and the brown residue obtained was purified by column chromatography on silica gel eluting with ethyl acetate/hexane mixtures.

General Procedure for [2+2+2] Cycloaddition Reactions Using Vollhardt's Catalyst (VC): To a refluxing solution of the diyne building block (0.1 mmol) in toluene/octane containing $CpCo(CO)_2$ (0.3 μL), a solution of the monoyne in the same solvent, also containing $CpCo(CO)_2$, was added under nitrogen over a period of 6−10 h (syringe pump). The reaction flask was connected to a vacuum distillation set-up and all volatiles were subsequently distilled off to leave the crude product. The dark oily residue was chromatographed on a silica gel column eluting with petroloeum ether/ethyl acetate mixtures to give the co-trimerized product.

Acknowledgments

We thank the DST, New Delhi, for financial support. We are grateful to the RSIC, Mumbai, in particular to Professor A. Srikrishna for recording the spectra. N. S. thanks the CSIR, New Delhi, for the award of a research fellowship.

[1] J. Gunte, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699.
[2] A. Giannis, T. Kolter, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244.
[3] V. J. Hruby, *Biopolymers* **1993**, *33*, 1073.
[4] D. F. Ortwine, T. C. Malaone, C. F. Bigge, J. T. Drummond, C. Humblet, C. Johnson, G. W. Pinnter, *J. Med. Chem.* **1992**, *35*, 1345.
[5] R. M. J. Liskamp, *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 1.
[6] V. J. Hruby, W. L. Cody, A. M. D. Castrucci, M. E. Hadley, *Collect. Czech. Chem. Commun.* **1988**, *53*, 2549; H. Nakagawa, N. Nihomatsu, S. Ohta, M. Hirobe, *Biochem. Biophys. Res. Commun.* **1996**, *225*, 1027; P. A. Temussi, S. Salvadori, P. Amodeo, C. Bianchi, R. Guerrini, R. Tomatis, L. H. Lazarus, D. Picone, T. Tancredi, *Biochem. Biophys. Res. Commun.* **1994**, *198*, 933; S. E. Gibson (née Thomas), N. Guillo, M. J. Tozer, *Tetrahedron* **1999**, *55*, 585; P. L. Ornstein, D. D. Schoepp, M. B. Arnold, N. K. Augenstein, D. Lodge, J. D. Millar, J. Chambers, J. W. Parchal, D. M. Zimmerman, J. D. Leander, *J. Med. Chem.* **1992**, *35*, 3545; P. W. Shiller, T. M.-D. Nguyen, G. Weltrowska, B. C. Wilkes, B. J. Marsden, C. Lemieux, N. N. Chung, *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 11871; W. M. Kazmierski, Z. Urbanczyk-Lipkowska, V. J. Hruby, *J. Org. Chem.* **1994**, *59*, 1789.
[7] F.-F. Clerc, J.-D. Guitton, N. Fromage, Y. Lelievre, M. Duchesne, B. Toeque, E. James-Surcouf, A. Commercon, J. Becquart, *Bioorg. Med. Chem.* **1995**, *5*, 1779 ; G. Byk, Y. Lelievre, M. Duchesne, F.-F. Clerc, D. Scherman, J.-D. Guitton, *Bioorg. Med. Chem. Lett.* **1997**, *5*, 115.
[8] E. C. Griffiths, in: *A Text Book of Drug Design and Development* (Eds.: P. Krogsgaard-Larsen, H. Bundgaard), Harwood Academic Publishers, Tokyo, **1992**, pp. 487−528.
[9] A. Pictet, T. Spengler, *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030; A. Brossi, A. Focella, S. Teitel, *Helv. Chim. Acta* **1972**, *55*, 15; H. Kahno, Y. Sekine, *Heterocycles* **1996**, *42*, 141; H. G. Chen, O. P. Goel, *Synth. Commun.* **1995**, *25*, 49.
[10] W. M. Kazmierski, V. J. Hruby, *Tetrahedron Lett.* **1991**, *32*, 5769; W. M. Whaley, T. R. Govindachari, *Org. React.* **1951**, *6*, 74−150; W. D. F. Meutermans, P. F. Alewood, *Tetrahedron Lett.* **1995**, *36*, 7709; U. Schöllkopf, R. Hinrchs, R. Lonsky, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 143; J. M. Liu, J. J. Young, Y. J. Li, C. K. Sha, *J. Org. Chem.* **1986**, *51*, 1120.

[11] D. Seebach, E. Dziadulewicz, L. Behrendt, S. Cantoreggi, R. Fitzi, *Liebigs Ann. Chem.* **1989**, 1215; T. Kammermeier, U. Lerch, C. Sommer, *Synthesis* **1992**, 1157; C. Wang, H. I. Moseberg, *Tetrahedron Lett.* **1995**, *36*, 3623; E. A. Mash, L. J. Williams, S. S. Pfeiffer, *Tetrahedron Lett.* **1997**, *38*, 6977; J. Hiebl, H. Kollmann, S. H. Levinson, P. Offen, S. B. Shetzline, R. Badlani, *Tetrahedron Lett.* **1999**, *40*, 7935; R. Chinchilla, N. Galindo, C. Najera, *Synthesis* **1999**, 704.

[12] [12a] S. Kotha, E. Brahmachary, *Tetrahedron Lett.* **1997**, *38*, 3561. – [12b] S. Kotha, N. Sreenivasachary, E. Brahmachary, *Tetrahedron Lett.* **1998**, *39*, 2805. – [12c] S. Kotha, E. Brahmachary, *J. Org. Chem.* **2000**, *65*, 1359. – [12d] S. Kotha, E. Brahmachary, N. Sreenivasachary, *Tetrahedron Lett.* **1998**, *39*, 4095. – [12e] S. Kotha, N. Sreenivasachary, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 257. – [12f] S. Kotha, N. Sreenivasachary, S. Halder, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2565. – [12g] S. Kotha, N. Sreenivasachary, E. Brahmachary, *Eur. J. Org. Chem.* **2000**, 787.

[13] G. Stork, A. Y. W. Leong, A. M. Touzin, *J. Org. Chem.* **1976**, *21*, 3491; M. J. O'Donnell, R. L. Polt, *J. Org. Chem.* **1982**, *47*, 2663; M. Moreno-Manas, R. Plexitats, A. Roglans, *Liebigs Ann.* **1995**, 1807.

[14] M. Schuster, S. Blechert, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036, and in: *Alkene Metathesis in Organic Synthesis* (Ed.: A. Furstner), Springer, Berlin, **1998**; H.-G. Schmalz, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1833; N. Chatani, T. Morimoto, T. Muto, S. Murai, *J. Am. Chem. Soc.* **1994**, *116*, 6049; A. Kinoshita, M. Mori, *Synlett* **1994**, 1020; R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446; S.-H. Kim, N. Bowden, R. H. Grubbs, *J. Am. Chem. Soc.* **1994**, *116*, 10801; R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413.

[15] M. E. Krafft, A. M. Wilson, O. A. Dasse, L. V. R. Bonaga, Y. Y. Cheung, Z. Fu, B. Shao, I. L. Scott, *Tetrahedron Lett.* **1998**, *39*, 5911.

[16] D. Seyferth, M. O. Nestle, A. T. Wehman, *J. Am. Chem. Soc.* **1975**, *97*, 7417; D. Seyferth, A. T. Wehman, *J. Am. Chem. Soc.* **1970**, *92*, 5522.

[17] G. L. Bolton, *Tetrahedron Lett.* **1996**, *37*, 3433; G. L. Bolton, J. C. Hodges, R. Rubin, *Tetrahedron* **1997**, *53*, 6611.

[18] T. Imanishi, N. Yagi, M. Hanaoka, *Tetrahedron Lett.* **1981**, *22*, 667.

[19] R. Grigg, R. Scott, P. Stevenson, *J. Chem. Soc., Perkin Trans. 1* **1988**, 1357.

[20] R. Grigg, R. Scott, P. Stevenson, *Tetrahedron Lett.* **1982**, *23*, 2691; B. Witulski, T. Stengel, *Angew. Chem. Int. Ed.* **1999**, *38*, 2426.

[21] C. J. Eaborn, *J. Organomet. Chem.* **1975**, *100*, 43; B. G. Felix, J. Dunogues, F. Pisciotti, R. Calas, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 488; L. A. Jacob, B.-L. Chen, D. Stec, *Synthesis* **1993**, 611; R. L. Funk, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1980**, *102*, 5253; R. L. Funk, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1980**, *102*, 5245; K. P. C. Vollhardt, *Pure. Appl. Chem.* **1993**, *65*, 153; F. Toda, P. Garratt, *Chem. Rev.* **1992**, *92*, 1685 and references cited therein.

[22] Y. Sato, T. Nishimata, M. Mori, *Heterocycles* **1997**, *44*, 443; Y. Sato, T. Nishimata, M. Mori, *J. Org. Chem.* **1994**, *59*, 6133; S. Ikeda, H. Watanabe, Y. Sato, *J. Org. Chem.* **1998**, *63*, 7026.

[23] T.-Y. Hsiao, K. C. Santhosh, K.-F. Liou, C.-H. Cheng, *J. Am. Chem. Soc.* **1998**, *120*, 12232.

[24] Y. Yamamoto, H. Kitahara, R. Ogawa, K. Itoh, *J. Org. Chem.* **1998**, *63*, 9610.

[25] Y. Yamamoto, A. Nagata, K. Itoh, *Tetrahedron Lett.* **1999**, *40*, 5035.

[26] A. C. Williams, P. Sheffels, L. T. Sheehan, *Organometallics* **1989**, *8*, 1566; K. Takai, M. Yamada, K. Utimoto, *Chem. Lett.* **1995**, 851; V. A. Sergeev, Yu. A. Chernomordik, V. S. Kolesov, V. V. Gavrilenko, V. V. Korshak, *J. Org. Chem. USSR (Engl. Transl.)* **1975**, *11*, 770; P. Caddy, M. Green, E. O'Brien, L. E. Smart, P. Woodward, *J. Chem. Soc., Dalton Trans.* **1980**, 962.

[27] L. A. Jacob, B.-L. Chen, D. Stec, *Synthesis* **1993**, 611; J. Dunogues, F. Pisciotti, R. Calas, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 488; C. J. Eaborn, *J. Organomet. Chem.* **1975**, *100*, 43.

[28] R. Tacke, in: *Organosilicon and Bioorganosilicon Chemistry* (Ed. H. Sakurai), John Wiley, New York, **1985**, pp. 251.

[29] R. J. Smith, S. Bratovanov, S. Bienz, *Tetrahedron* **1997**, *53*, 13695; R. Fitzi, D. Seebach, *Tetrahedron* **1988**, *44*, 5277; R. D. Walkup, D. C. Cole, B. R. Whittlesey, *J. Org. Chem.* **1995**, *60*, 2630; L. A. Jacob, B.-L. Chen, D. Stec, *Synthesis* **1993**, 611; S. R. Wilson, L. A. Jacob, *J. Org. Chem.* **1985**, *51*, 4833; M. Frankel, D. Gertner, A. Shenhar, A. Zilkha, *J. Chem. Soc.* **1963**, 5049.

Received January 15, 2001
[O01017]