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Asymmetric synthesis of the marine alkaloid (−)-(*S*)-nakinadine C

Stephen G. Davies *, Paul M. Roberts, Rushabh S. Shah, James E. Thomson

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK

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ABSTRACT

The first asymmetric synthesis of the marine alkaloid (−)-(*S*)-nakinadine C is described. This synthesis employs the conjugate addition of lithium dibenzylamide to an *N*-α-phenylacryloyl SuperQuat derivative followed by diastereoselective protonation of the intermediate enolate using 2-pyridone as the key step to introduce the stereochemistry. (−)-(*S*)-Nakinadine C was isolated in 13% yield over 9 steps from commercially available atropic acid, 98:2 dr [(*Z*):(*E*) ratio] and >99% ee.

Sea creatures have proven to be a rich source of structurally diverse natural products: the wealth of molecular architectures of marine origin displaying desirable biological activity continues to inspire and fascinate chemists and biologists alike.[1] A structurally unique bis-pyridine alkaloid was isolated from the sponge *Amphimedon* sp. in 2007 by Kobayashi and co-workers, and was named nakinadine A.[2] Soon after, in 2008, the isolation and characterisation of a further five members of the nakinadine family (nakinadines B–F) were reported by Kobayashi and co-workers.[3] In each case, the atom connectivity (and hence structure) of these new alkaloids was assigned predominantly on the basis of NMR spectroscopic and mass spectrometric studies. Nakinadine B and nakinadine C were determined to comprise a common 2-phenyl-3-aminopropanoic acid core differentiated by a long *N*-alkyl side-chain capped with a pyridin-3-yl substituent. Kobayashi and co-workers assigned the absolute (*S*)-configuration to both of these alkaloids by application of a derivatisation method.[3,4] In a biological assay, nakinadines A–C demonstrated cytotoxicity against L1210 murine leukaemia and KB human epidermoid carcinoma cells[2,3] (Fig. 1).

To date, the only reported synthesis of any of the nakinadine alkaloids is our asymmetric synthesis of (−)-(*S*)-nakinadine B from atropic acid (**1**).[5] Atropic acid (**1**) was converted into the corresponding anhydride, which was reacted with the lithium anion of D-valine derived SuperQuat **2**[6,7] to give **3** in 72% yield. The key step, conjugate addition of lithium dibenzylamide to **3** with in situ diastereoselective enolate protonation with 2-pyridone, gave an 87:13 mixture of the corresponding *N*-β-aminoacryloyl SuperQuats.[8] After chemoselective mono-N-debenzylation,[9] this gave an 87:13 mixture of **4** and **5**, which were isolated in 73% and 9% yield, respectively. Subsequent elaboration of the major product **4** via reductive N-alkylation and oxidative N-debenzylation gave **6** in 60% yield, and hydrolysis of **6** via a three-step procedure involving *N*-Boc protection, hydrolysis with LiOOH and *N*-Boc deprotection gave (−)-(*S*)-nakinadine B (**7**) in 55% yield [17% yield over 9 steps from atropic acid (**1**)] and >99% ee (Scheme 1).[5] Herein we report the application of this approach to the first asymmetric synthesis of (−)-(*S*)-nakinadine C. A full and detailed comparison of the characterisation data reported for the natural product with that recorded for the synthetic material is also undertaken, which enables confirmation of the reported structure of the natural product.

The structural similarities of nakinadine B and nakinadine C suggested that a common route could be employed for their synthesis from **4**. The requisite long-chain aldehyde **15** required for the synthesis of nakinadine C was prepared via initial protection of 11-bromoundecan-1-ol (**8**) as the corresponding THP ether **9** followed by treatment with PPh_3 to give the intermediate phosphonium bromide salt **10**.[10] Addition of KHMDS to **10** followed by aldehyde **12** (which was prepared via Swern oxidation of commercially available alcohol **11**, and used immediately) gave **13** as a 97:3 mixture of (*Z*):(*E*) olefin isomers,[10,11] which were isolated in 45% combined yield (in 3 steps from **8**). Removal of the *O*-THP protecting group gave alcohol **14** in 85% yield and 96:4 (*Z*):(*E*) ratio.[10,11] IBX oxidation[12] of alcohol **14** (as required) gave aldehyde **15**, which was used immediately in the next step (Scheme 2).

Reductive N-alkylation of secondary amine **4** with a freshly prepared sample of aldehyde **15** gave tertiary amine **16** in 80% yield and 97:3 (*Z*):(*E*) ratio,[11] with subsequent oxidative N-debenzylation with CAN[9] giving secondary amine **18** in 70% isolated yield and 96:4 (*Z*):(*E*) ratio.[11] In order to establish that competing

* Corresponding author.
E-mail address: steve.davies@chem.ox.ac.uk (S.G. Davies).

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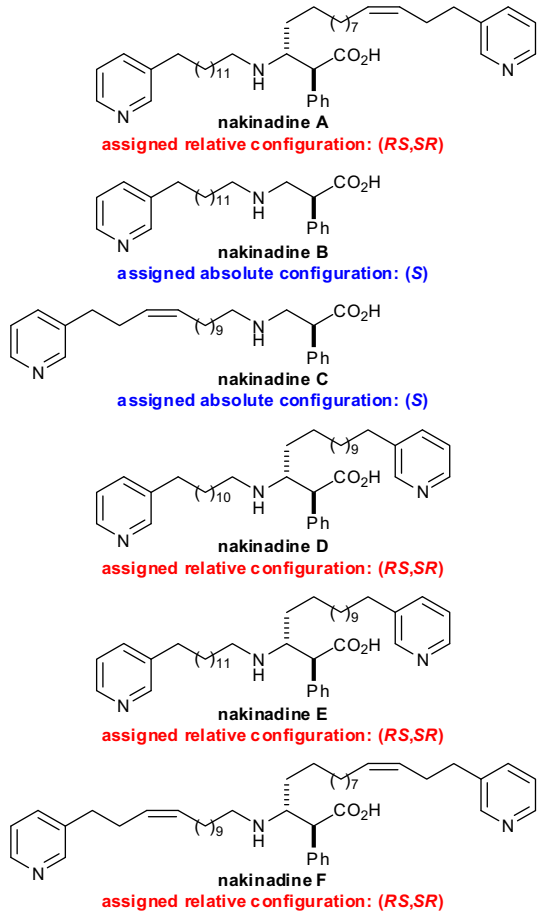
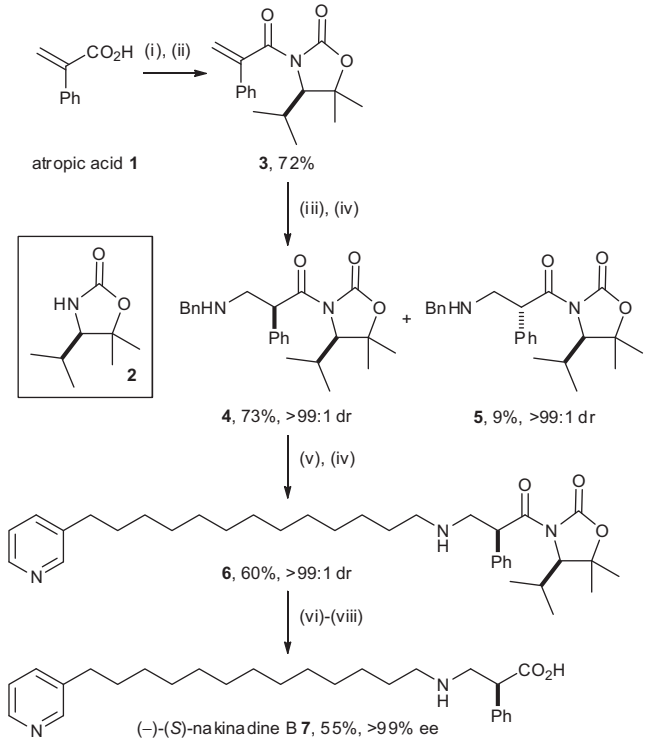


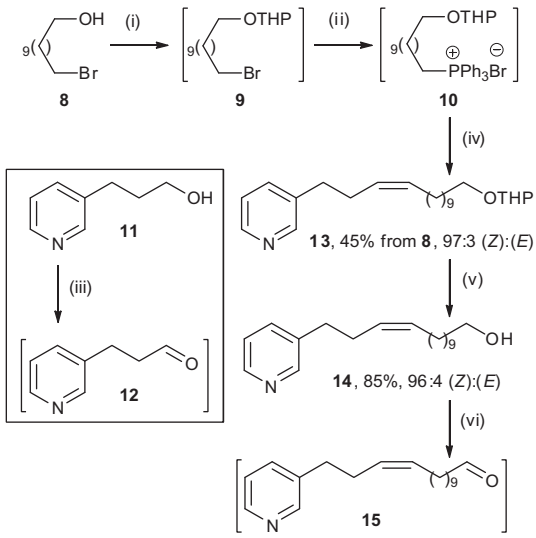
Figure 1. Assigned structures, relative and absolute configurations of nakinadines A–F.

epimerisation had not occurred during conversion of **4** into **18**, authentic samples of the epimeric compounds **17** and **19** were prepared from **5** via an analogous sequence of reactions. Hydrolysis of **18** via the optimised three-step procedure gave a sample of (*S*)-**20** {$[\alpha]_D^{20}$ −5.9 (*c* 1.0 in $CHCl_3$)},[13] the reported structure of nakinadine C,[3] in 45% yield over the 3 steps [representing 13% overall yield in 9 steps from atropic acid (**1**)] and 98:2 (*Z*):(*E*) ratio,[11] with SuperQuat **2** {$[\alpha]_D^{20}$ −23.6 (*c* 1.0 in $CHCl_3$); lit.[14] $[\alpha]_D^{23}$ −24.2 (*c* 1.0 in $CHCl_3$)} being recovered in 73% isolated yield over the 3 steps. Similarly, hydrolysis of **19** (in 3 steps) gave (*R*)-**20** {$[\alpha]_D^{20}$ +5.8 (*c* 1.0 in $CHCl_3$)}[13] in 48% yield over the 3 steps and 95:5 (*Z*):(*E*) ratio;[11] SuperQuat **2** {$[\alpha]_D^{20}$ −24.1 (*c* 1.0 in $CHCl_3$)} was recovered in 63% isolated yield over the 3 steps. The samples of (*S*)-**20** and (*R*)-**20** were each determined to be >99% ee by conversion into the corresponding methyl ester upon treatment with $SOCl_2$ in MeOH, subsequent conversion into the corresponding Mosher's amides, and analysis by ^1H and ^{19}F NMR spectroscopy.[15] This demonstrates that neither hydrolysis reaction (of **18** or **19**) nor the esterification of **20** are accompanied by competing epimerisation/racemization (Scheme 3).

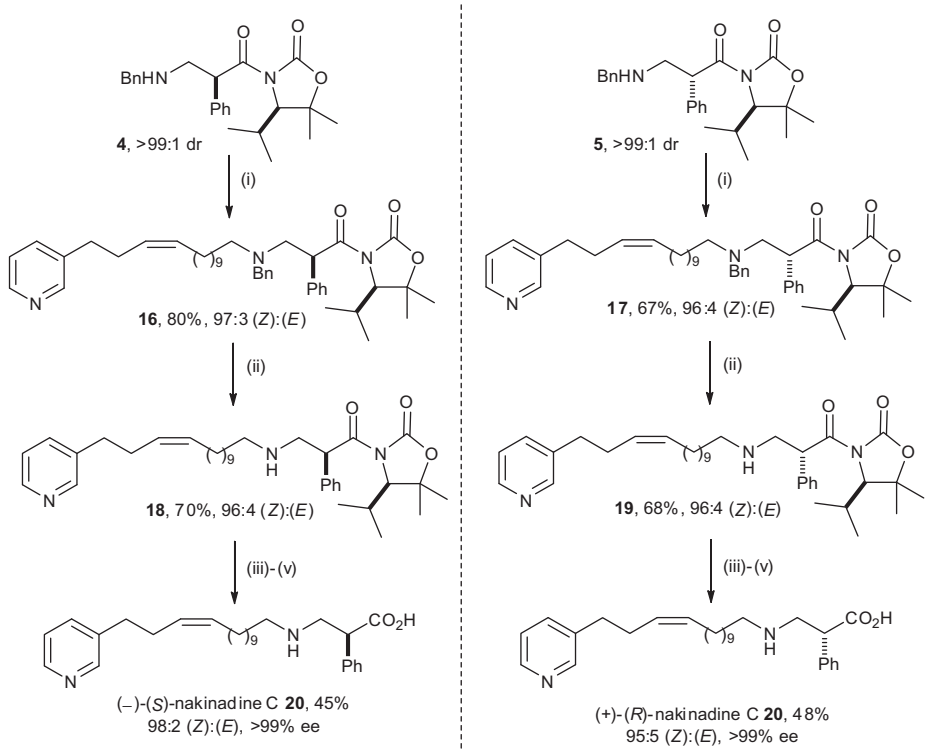
A detailed comparison of the characterisation data obtained for (*S*)-**20** with those for the material derived from the natural source, reported by Kobayashi and co-workers,[3] was undertaken next.[13] Both the UV trace and the ESI MS/MS fragmentation pattern for (*S*)-**20** proved to be essentially identical to those reported for the natural product, with the exception that the ESI MS/MS fragmentation pattern for the natural product was reported to include an ion at *m*/*z* 287, which was attributed to $C_{19}H_{31}N_2^+$ (i.e., $ArC_{14}H_{26}NH^+$ where Ar = pyridin-3-yl), but the synthetic material (*S*)-**20** gave an ion at *m*/*z* 289, consistent with the fragment $C_{19}H_{33}N_2^+$ (i.e., $ArC_{14}H_{26}NH_3^+$ where Ar = pyridin-3-yl). The IR spectroscopic data reported for natural nakinadine C included absorption bands at 1733 cm^{-1} and 2900–3400 cm^{-1}, although these absorptions are not characteristic of a zwitterionic amino acid.[16] Analysis of (*S*)-**20** by IR spectroscopy produced no significant absorptions around 1730 cm^{-1} but strong absorption bands at 1564 and 1653 cm^{-1}, which are characteristic of a bending vibration of the ammonium functionality and a stretching vibration of the carboxylate



Scheme 1. Reagents and conditions: (i) pivaloyl chloride, Et_3N, THF, 0 °C, 1 h; (ii) **2**, BuLi, THF, −78 °C to rt, 2 h; (iii) $LiNBn_2$, THF, −78 °C, 4 h, then 2-pyridone, −78 °C to rt, 16 h; (iv) CAN, MeCN, H_2O, rt, 16 h; (v) 13-(pyridin-3′-yl)tridecanal, $NaB(OAc)_3H$, AcOH, DCE, rt, 16 h; (vi) Boc_2O, $NaHCO_3$, EtOH, 0 °C to rt, 16 h; (vii) LiOH, aq H_2O_2, THF, 0 °C to rt, 16 h; (viii) HCl (2 M in Et_2O), rt, 30 min.



Scheme 2. Reagents and conditions: (i) DHP, PPTS, CH_2Cl_2, rt, 16 h; (ii) PPh_3, MeCN, reflux, 48 h; (iii) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, 40 min, then Et_3N, −78 °C to rt, 90 min; (iv) KHMDS, **12**, THF, −78 °C to rt, 3 h; (v) HCl (3 M aq), MeOH, rt, 16 h; (vi) IBX, EtOAc, 80 °C, 3 h.



Scheme 3. Reagents and conditions: (i) **15**, $NaB(OAc)_3H$, AcOH, DCE, rt, 16 h; (ii) CAN, MeCN, H_2O, rt, 16 h; (iii) Boc_2O, $NaHCO_3$, EtOH, 0 °C to rt, 16 h; (iv) LiOH, aq H_2O_2, THF, 0 °C to rt, 16 h; (v) HCl (2 M in Et_2O), rt, 30 min.

	Natural Nakinadine C	Synthetic (*S*)-**20**
Appearance	colourless oil	white solid (mp 124-125 °C)
$[\alpha]_D$	*not reported*	$[\alpha]_D^{20}$ –5.9 (*c* 1.0 in $CHCl_3$)
λ_{max} (10^{-2} ε)	258 (32), 263 (33), 269 (30)	258 (35), 263 (40), 269 (29)
ν_{max}	3350, 3200, 2920, 1733	3030, 2923, 2852, 1653, 1564

Figure 2A. Selected physical and spectroscopic data for natural nakinadine C and synthetic (*S*)-**20**. UV absorption data for (*S*)-**20** were recorded in MeOH (λ_{max} in nm, ε in L mol^{-1} cm^{-1}); IR absorption data for (*S*)-**20** were recorded using an ATR module (ν_{max} in cm^{-1}).

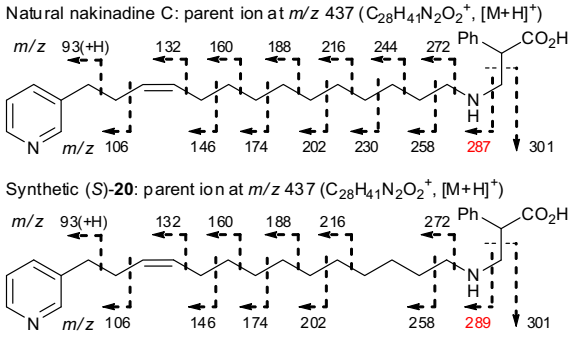
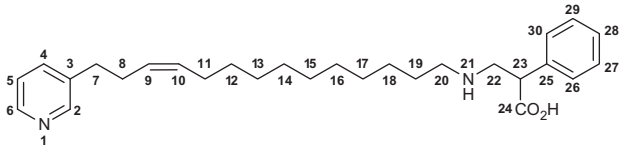


Figure 2B. ESI MS/MS fragmentation pattern for natural nakinadine C and synthetic (*S*)-**20**.

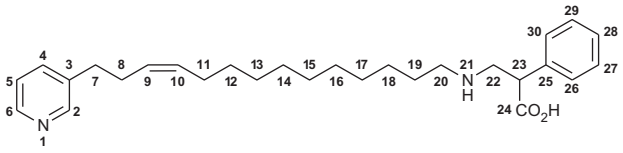
functionality, respectively, within a zwitterionic amino acid[16] (Figs. 2A and 2B). Addition of HCl to the sample of (*S*)-**20** and acquisition of an IR spectrum did show an absorption band at 1721 cm^{-1}, however. The IR absorption values of (*S*)-**20** and the corresponding HCl salt are entirely in accord with those for over 200 examples of zwitterionic β-amino acids and the corresponding ammonium salts that have been synthesised within our laboratory.[17] Analogous differences were noted in comparison of the



	Proton #	Nakinadine C 600 MHz δ_H (ppm)	(*S*)-**20** 500 MHz δ_H (ppm)
pyridin-3-yl moiety	2-H, 6-H	8.44 (2H, m)	8.44 (2H, m)
	4-H	7.49 (1H, m)	7.50 (1H, app dt)
	5-H	7.18 (1H, m)	7.19 (1H, dd)
alkyl chain	7-H_2	2.65 (2H, t)	2.66 (2H, t)
	8-H_2	2.35 (2H, dt)	2.36 (2H, app q)
	9-H, 10-H	5.37 (2H, m)	5.39 (2H, m)
	11-H_2	1.92 (2H, dt)	1.93 (2H, app q)
	12-18-H_2	1.2 (14H, m)	1.26 (14H, m)
	19-H_2	1.61 (2H, br s)	1.66 (2H, m)
	20-H_2	2.84 (3H, m)*	2.99 (2H, m)
β-amino acid moiety	22-H_A	2.84 (3H, m)*	2.85 (1H, dd)
	22-H_B	3.49 (1H, br s)	3.42 (1H, app t)
	23-H	4.11 (1H, br s)	4.04 (1H, dd)
phenyl ring	26-H, 30-H	7.33 (2H, m)	7.38 (2H, app d)
	27-H, 29-H	7.25 (2H, m)	7.30 (2H, app t)
	28-H	7.20 (1H, m)	7.23 (1H, app t)

Figure 3. ^{1}H NMR spectroscopic data for natural nakinadine C (unknown concentration in $CDCl_3$) and synthetic (*S*)-**20** (127 mM in $CDCl_3$). For purposes of comparison, the numbering convention adopted by Kobayashi and co-workers. (see Ref. 3) has also been adopted here. *The (unassigned) ^{1}H NMR data for the natural product includes resonances at 2.82 (2H, br s) and 2.86 (1H, br s); the mid-point of these has been quoted here for purposes of comparison.

ESI MS/MS fragmentation and IR spectroscopic data for (*S*)-**7** (our synthetic sample of nakinadine B) with those reported for the natural product.[5]



	Carbon #	Nakinadine C 150 MHz δ_C (ppm)	(*S*)-**20** 125 MHz δ_C (ppm)
pyridin-3-yl moiety	2 (CH)	149.9	150.0
	3 (C)	137.3	137.2
	4 (CH)	135.8	135.9
	5 (CH)	123.2	123.2
	6 (CH)	147.2	147.3
alkyl chain	7 (CH_2)	33.0	33.0
	8 (CH_2)	28.7	28.7
	9 (CH)	127.7	127.7
	10 (CH)	131.4	131.4
	11 (CH_2)	27.2	27.2
	12-18 (CH_2)	26.7, 29-30	26.9, 29-30
	19 (CH_2)	29-30	25.4
	20 (CH_2)	47.9	47.6
β-amino acid moiety	22 (CH_2)	50.8	51.1
	23 (CH)	51.1	51.8
	24 (C)	176.7	176.4
phenyl ring	25 (C)	135.8	139.0
	26, 30 (CH)	128.2	128.2
	27, 29 (CH)	128.7	128.8
	28 (CH)	127.3	127.2

Figure 4. ^{13}C NMR spectroscopic data for natural nakinadine C (unknown concentration in $CDCl_3$) and synthetic (*S*)-**20** (127 mM in $CDCl_3$). For purposes of comparison, the numbering convention adopted by Kobayashi and co-workers. (see Ref. 3) has also been adopted here.

Comparison of the ^1H NMR spectroscopic data of (*S*)-**20** (127 mM in $CDCl_3$) with those reported for natural nakinadine C (unknown concentration in $CDCl_3$)[18] gave excellent agreement (Fig. 3),[19] whilst similar comparison of the ^{13}C NMR data showed generally excellent agreement,[18] with most values having $|\Delta\delta| \leqslant 0.3$ ppm[20] (Fig. 4). Larger differences were observed for *C*(19) [$|\Delta\delta| \sim 4$ ppm],[20] *C*(23) [$|\Delta\delta|$ 0.7 ppm][20] and *C*(25) [$|\Delta\delta|$ 3.2 ppm].[20,21] Although the origin of these differences is unclear, the structural assignment of **20** is secure.

In conclusion, an efficient asymmetric synthesis of the marine alkaloid (−)-(*S*)-nakinadine C has been developed, using a strategy reliant upon conjugate addition of lithium dibenzylamide to an *N*-α-phenylacryloyl SuperQuat derivative followed by diastereoselective protonation of the intermediate enolate using 2-pyridone as the key step to introduce the stereochemistry. This synthesis proceeds over 9 steps from commercially available atropic acid in 13% overall yield, delivering the natural product as a 98:2 mixture of (*Z*):(*E*) diastereoisomers in >99% ee. Further investigations into the development of efficient asymmetric syntheses of the remaining members of the nakinadine family of alkaloids are ongoing within our laboratory.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.043.

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18. Resonances in the ^1H and ^{13}C NMR spectra of the natural product were not fully assigned by Kobayashi and co-workers; they are assigned here by closest comparison. The resonance at δ_C 26.7 ppm for the natural product was, however, assigned as being due to *C*(11); this assignment has been revised here on the basis of the extensive NMR spectroscopic data obtained for (*S*)-**20**.
19. In contrast, the hydrochloride salt (*S*)-**2**·HCl proved to be only sparingly soluble in $CDCl_3$ and produced a broad ^1H NMR spectrum; the chemical shift values did not correspond well with those reported for the natural product.
20. $|\Delta\delta|$ Refers to the absolute value of $(\delta_{natural}) - (\delta_{synthetic})$.
21. A similar phenomenon was observed when the ^{13}C NMR data for (*S*)-**7** (our synthetic sample of nakinadine B) were compared with those reported for natural nakinadine B (see Ref. 5): values showed generally excellent agreement [$|\Delta\delta| \leqslant 0.5$ ppm], although larger differences were noted for *C*(18), *C*(22) and *C*(24). Thus, in both nakinadine B and nakinadine C, these correspond to NCH_2CH_2 [*C*(18), nakinadine B; *C*(19), nakinadine C], NCH_2CHPh [*C*(22), nakinadine B; *C*(23), nakinadine C] and *i-Ph* [*C*(24), nakinadine B; *C*(25), nakinadine C]. Note also, $|\Delta\delta|$ >0.5 ppm for *C*(8) of nakinadine B; however the equivalent carbon atom in nakinadine C is in an allylic position so their environments (and hence chemical shift values) are not directly comparable.