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Total synthesis and absolute configuration of nocardioazine B†

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The first total synthesis of the indole alkaloid nocardioazine B was accomplished in 10 steps with an overall yield of 11.8%, establishing the absolute stereochemistry of the natural product.

Nocardioazines A and B are two unprecedented prenylated-diketopiperazine alkaloids isolated from a nonsaline liquid culture of *Nocardiopsis* sp. (CMB-M0232) recovered from a sediment sample of South Molle Island, near Brisbane, Australia.[1] The bridged scaffold of nocardioazine A revealed stronger inhibitory effects on the membrane protein efflux pump P-glycoprotein, reversing doxorubicin resistance in a multidrug resistant colon cancer cell. The structure and relative stereochemistry of nocardioazines were determined on the basis of extensive NMR spectral investigations, while their absolute configuration, as depicted in Fig. 1, is a prediction based on biosynthetic speculation.

As part of our program on the synthesis of marine secondary metabolites[2] we were interested in synthetic approaches toward the total synthesis of nocardioazines and selected nocardioazine B (**1**) as an initial entry into this interesting class of natural products.[3] Herein, we disclose the first total synthesis of nocardioazine B and the resulting assignment of the absolute configuration of the natural product.

As outlined retro-synthetically in Scheme 1, our synthetic approach relies on assembly of two main building blocks of comparable complexity, that is C(3)-quaternary-substituted pyrroloindolines **3** and **4**. Condensation of acid **3** with a free amine derived from **4** was envisioned to deliver the required precursor **2**. Further retrosynthetic analysis of the individual subunits revealed that they can be prepared from *N*′-bis(*tert*-butyloxycarbonyl)-D-tryptophan methyl ester **5** and *N*′-bis(*tert*-butyloxycarbonyl)-L-tryptophan methyl ester **7**.

The synthesis of pyrroloindoline **3** started with the preparation of bromohexahydropyrroloindole **8** from the readily available *N*′-bis(*tert*-butyloxycarbonyl)-D-tryptophan methyl ester **5**[4] (Scheme 2). Treatment of **5** with 1 equivalent of *N*-bromosuccinimide (NBS) and 1 equivalent of pyridinium *p*-toluenesulfonate (PPTS) in dichloromethane resulted in the formation of the *exo*-3a-bromo hexahydropyrrolo[2,3-*b*]indole **8** in 82% yield[5] and virtually as a single diastereoisomer.[6] Bromohexa-hydropyrroloindole **8** was then converted into methylhexahydropyrroloindole **10** employing a highly regio- and stereoselective intramolecular cyclopropanation/ring-opening protocol developed by Rainier and co-workers.[7] Thus, treatment of **8** with potassium *tert*-butoxide at 0 °C in THF afforded the corresponding cyclopropyl-azetoindoline **9** in 85% yield. Subsequent treatment of this donor–acceptor cyclopropane with trimethylaluminium at −40 °C in dichloromethane gave rise to the desired C(3)-methyl-substituted pyrroloindoline **10** in 70% yield. Saponification of **10** with lithium hydroxide next produced the key fragment **3**.

The success of trimethylaluminium additions to cyclopropylazetoindoline **9** encouraged us to explore similar reactions of allylic carbon nucleophiles with cyclopropylazetoindoline, aiming for the construction of pyrroloindoline **4**.

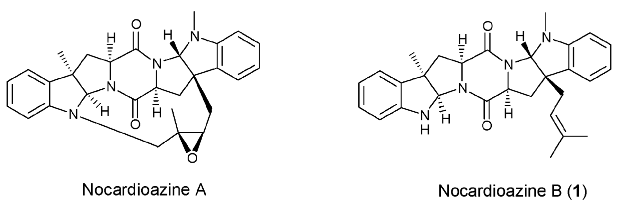

Fig. 1 Structures of nocardioazines A and B.

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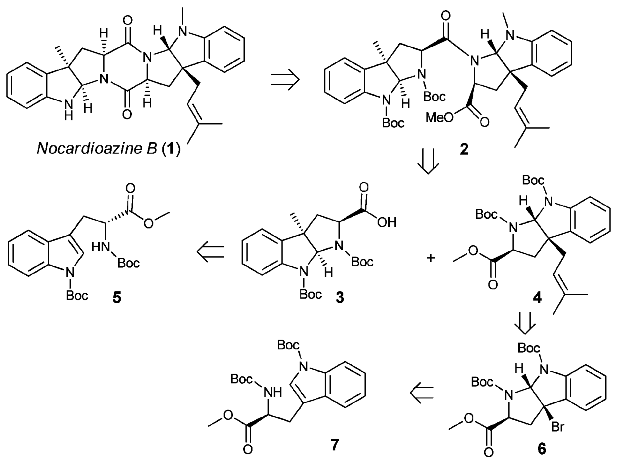
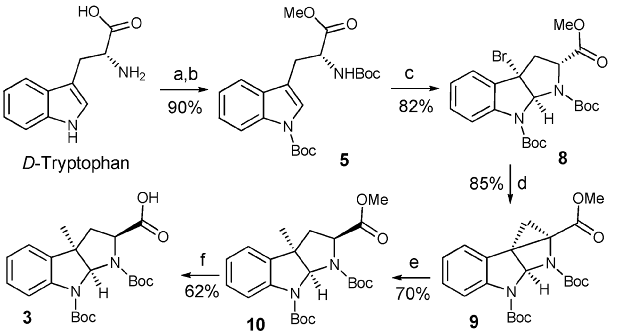
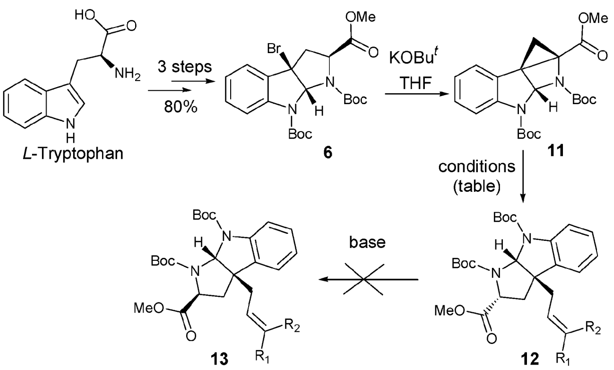
† Electronic supplementary information (ESI) available: Full details of experimental procedures for compounds **1–4**, **9–10**, **12**, **15–22** and ^{1}H NMR, ^{13}C NMR spectra for compounds**1–4**, **9–10**, **12**, **15–16** and **18–22**. See DOI: 10.1039/c2cc31025b



Scheme 1 Retrosynthetic analysis of nocardioazine B (**1**).



Scheme 2 (a) MeOH–HCl; (b) Boc_2O, CH_2Cl_2, NaOH, Bu_4NHSO_4; (c) NBS, CH_2Cl_2, 0 °C; (d) $KOBu^t$, THF, 0 °C; (e) $AlMe_3$, CH_2Cl_2, −40 °C; (f) LiOH, THF, MeOH–H_2O.

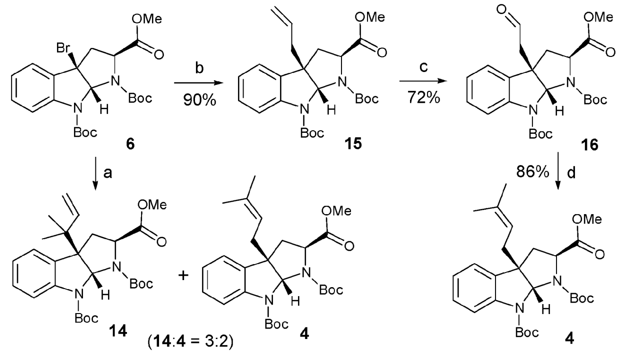


Entry	Conditions		Yield	R_1	R_2
1	Prenylmagnesium bromide,	CuCN, THF	0	CH_3	CH_3
2	Allylmagnesium bromide,	CuCN, THF	0	H	H
3	Allyltributylstannane	$BF_3{\cdot}Et_2O$, CH_2Cl_2	0	H	H
4	Allylzinc bromide	THF	30%	H	H
5	Prenylzinc bromide	THF	0	CH_3	CH_3

Scheme 3 Attempted synthesis of fragment **4**.

exo-3a-Bromo hexahydropyrrolo[2,3-*b*]indole **6** was prepared from L-tryptophan according to an identical procedure as described for **8**. In the event, treatment of cyclopropylazetoindoline **11**,[7] derived from bromohexahydro-pyrroloindole **6**, with various allylic carbon nucleophiles met with somewhat limited success (Scheme 3). The desired C(3)-allyl-substituted pyrroloindoline **12** was obtained in 30% yield only when allylzinc bromide (entry 4) was used as the nucleophile. The stereocenter adjacent to the carboxylate group of **12** has the incorrect stereochemistry relative to the key fragment **4**, so epimerization was required. Unfortunately, our effort to epimerize **12** to **13** under a variety of conditions (*e.g.*, LDA, $KOBu^t$, NaOMe) was not successful.

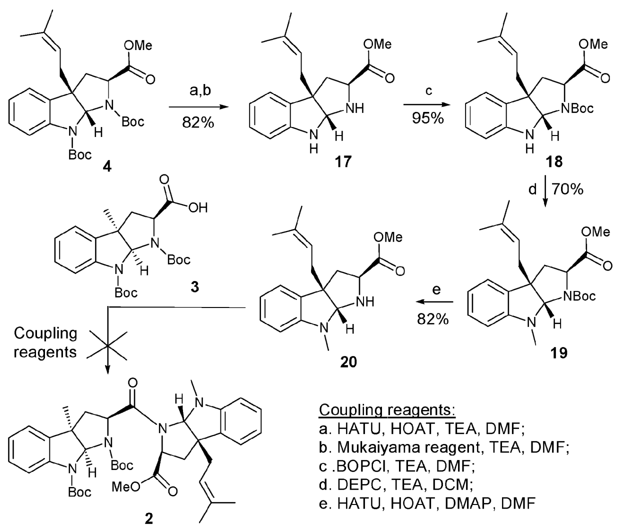
Due to the difficulties in the synthesis and epimerization of C(3)-allyl-substituted pyrroloindoline **12** using a cyclopropanation/ring-opening based approach, we altered our synthetic route by introducing the prenyl moiety to bromohexahydropyrroloindole **6** *via* either a direct radical prenylation process or a three-step sequence including a radical allylation, alkene cleavage and Wittig olefination.[8] Thus, reaction of **6** with prenyltributyltin in the presence of the free radical initiator AIBN in refluxing benzene produced the angular prenyl derivative **4** and the reverse prenyl **14** as an inseparable mixture. We next turned our attention to the stepwise strategy for the construction of the key intermediate **4**.



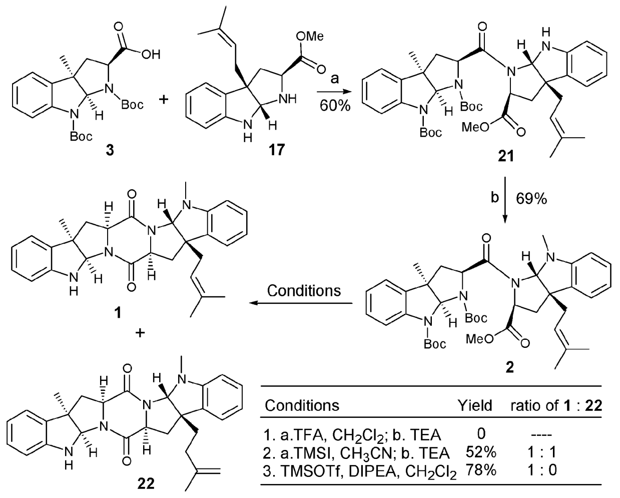
Scheme 4 (a) Prenyltributyltin, AIBN, C_6H_6; (b) allyltributyltin, AIBN, C_6H_6, reflux; (c) OsO_4, $NaIO_4$, lutidine; (d) $Ph_3P^+Pr^iBr^-$, *n*-BuLi, THF. AIBN: azobisisobutyronitrile.

In the event, treatment of **6** with allyltributyltin in the presence of AIBN in refluxing benzene afforded the corresponding allyl derivative **15** in 90% isolated yield. The terminal alkene in **15** was oxidatively cleaved through the action of OsO_4–$NaIO_4$ in the presence of 2,6-lutidine[9] to yield the corresponding aldehyde **16**, which was immediately subjected to a Wittig reaction with isopropylidenetriphenyl-phosphorane to produce **4**, with the complete prenyl side chain, in 86% yield (Scheme 4).[8a]

With the two key fragments in hand, the stage was now set for their assembly and elaboration into nocardioazine B. The two Boc carbamates of **4** were removed by the action of iodotrimethylsilane (TMSI)[10] to give rise to the doubly deprotected ester **17**,[11] which was then reprotected as its Boc derivative **18** in 78% overall yield (Scheme 5). Reductive methylation of **18** with $NaCNBH_3$ in the presence of aqueous HCHO and AcOH effected the N-methylation to produce **19** in 70% yield.[12] Removal of the *N*-Boc group with iodotrimethylsilane revealed the corresponding free amine **20**, which was then set the stage for fragment coupling. Unfortunately, all attempts to effect condensation of acid **3** with amine **20** under the influence of various coupling



Scheme 5 (a) TMSI, CH_3CN; (b) Et_3N, rt; (c) Boc_2O, THF; (d) HCHO (aq.), HOAc; $NaBH_3CN$, CH_3OH; (e) TMSI, CH_3CN; Et_3N, rt TMSI: trimethylsilyl iodide; HATU: 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOAT: 1-hydroxy-7-azabenzotriazole; BOPCl: bis(2-oxo-3-oxazolidinyl)phosphinic chloride; DEPC: diethyl cyanophosphonate.



Conditions	Yield	ratio of 1 : 22
1. a.TFA, CH_2Cl_2; b. TEA	0	----
2. a.TMSI, CH_3CN; b. TEA	52%	1 : 1
3. TMSOTf, DIPEA, CH_2Cl_2	78%	1 : 0

Scheme 6 (a) HATU, HOAT, DMF, TEA; (b) HCHO(aq.), HOAc, $NaBH_3CN$, CH_3OH.

reagents/conditions did not succeed. The failure to undergo the expected coupling reaction is presumably attributed to steric effects exerted by the *N*-methyl group in **20**.

The rate of fragment condensation should be facilitated by using a less sterically demanding nucleophile. Accordingly, we decided to couple the acid portion (**3**) directly to ester **17** and postpone the N-methylation to a later stage in the synthesis. Thus, addition of HATU, HOAT and triethylamine to a solution of acid **3** and amine **17** in DMF provided **21** in 60% yield (Scheme 6). Reductive N-methylation of **21** by an identical procedure as described for **19** gave rise to precursor **2** in 69% yield, which set to the stage for the final diketopiperazine formation. Literature precedent suggested that diketopiperazine formation could be a spontaneous process.[13] Several attempts at the direct formation of diketopiperazine from **2** were explored. Thus, treatment of **2** with trifluoroacetic acid in dichloromethane followed by neutralization with excess triethylamine failed to generate the corresponding diketopiperazine. On the other hand, TMSI-mediated[4] cleavage of the two Boc carbamates of **2** accompanied by cyclisation of the carbomethoxy function onto the proximal NH group produced a mixture of nocardioazine B (**1**) and the double bond isomerized analogue **22** as an inseparable 1 : 1 mixture in 52% combined yield. Gratifyingly, upon treatment of **2** with TMSOTf in the presence of DIPEA, nocardioazine B (**1**) can be obtained as a single isomer in 78% yield (Scheme 6).

The synthetic material displayed ^{1}H and ^{13}C NMR spectra identical to those reported by Capon and co-workers.[1] The optical rotation of synthetic **1**, $[\alpha]_D^{25} = -20$ (c 0.1, CH_3OH), was of comparable in magnitude but opposite in sign to that reported for the natural product, $[\alpha]_D^{25} = +17$ (c 0.04, CH_3OH), establishing the absolute configuration of the nocardioazine B (Fig. 2) as enantiomeric to what is shown in Fig. 1.

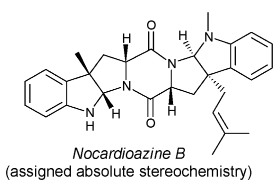


Fig. 2 Absolute configuration of nocardioazine B.

In summary, we have accomplished the total synthesis of nocardioazine B from tryptophan in 11.8% overall yield with the longest linear sequence of 10 steps. This synthesis established the absolute stereochemistry of the natural product. The extension of this chemistry towards the total synthesis of nocardioazine A and novel nocardioazine analogues for biological evaluation is under way and will be reported in due course.

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Notes and references

1 R. Raju, A. M. Piggott, X. C. Huang and R. J. Capon, *Org. Lett.*, 2011, **13**, 2770–2773.
2 (*a*) L. Wang, Z. S. Xu and T. Ye, *Org. Lett.*, 2011, **13**, 2506–2509; (*b*) H. Liu, Y. Q. Liu, Z. S. Xu and T. Ye, *Chem. Commun.*, 2010, **46**, 7486–7488; (*c*) X. G. Gao, Y. Q. Liu, S. Q. Kwong, Z. X. Xu and T. Ye, *Org. Lett.*, 2010, **12**, 3018–3021; (*d*) S. Li, Z. Chen, Z. S. Xu and T. Ye, *Chem. Commun.*, 2010, **46**, 4773–4775; (*e*) Z. Chen, L. Song, Z. S. Xu and T. Ye, *Org. Lett.*, 2010, **12**, 2036–2039; (*f*) Y. Jin, Y. Q. Liu, Z. Wang, S. Q. Kwong, Z. S. Xu and T. Ye, *Org. Lett.*, 2010, **12**, 1100–1103; (*g*) S. Liang, Z. S. Xu and T. Ye, *Chem. Commun.*, 2010, **46**, 153–155; (*h*) B. Chen, L. Dai, H. Zhang, W. Tan, Z. S. Xu and T. Ye, *Chem. Commun.*, 2010, **46**, 574–576; (*i*) S. Li, S. Liang, W. Tan, Z. S. Xu and T. Ye, *Tetrahedron*, 2009, **65**, 2695–2702; (*j*) S. Li, S. Liang, Z. S. Xu and T. Ye, *Synlett*, 2008, 569–574; (*k*) Q. Ren, L. Dai, H. Zhang, W. Tan, Z. S. Xu and T. Ye, *Synlett*, 2008, 2379–2383; (*l*) Z. Y. Chen and T. Ye, *New J. Chem.*, 2006, **30**, 518–520; (*m*) H. W. Pang, Z. S. Xu, Z. Y. Chen and T. Ye, *Lett. Org. Chem.*, 2005, **2**, 699–702; (*n*) H. W. Pang, Z. S. Xu and T. Ye, *Lett. Org. Chem.*, 2005, **2**, 703–706; (*o*) H. Chen, Z. S. Xu and T. Ye, *Tetrahedron*, 2005, **61**, 11132–11140; (*p*) Z. Y. Chen, J. G. Deng and T. Ye, *ARKIVOC*, 2003, 268–285; (*q*) Y. G. Peng, H. W. Pang and T. Ye, *Org. Lett.*, 2004, **6**, 3781–3784; (*r*) Z. S. Xu, Y. G. Peng and T. Ye, *Org. Lett.*, 2003, **5**, 2821–2824.
3 (*a*) K. Ishida, H. Matsuda, M. Murakami and K. Yamaguch, *Tetrahedron*, 1996, **52**, 9025–9030; (*b*) F. S. Guzman and J. B. Glober, *J. Nat. Prod.*, 1992, **55**, 931–939; (*c*) P. R. Sanchis, S. A. Savina, F. Albericio and M. Álvarez, *Chem.–Eur. J.*, 2011, **17**, 1388–1408.
4 M. K. Depew, S. P. Marsden, D. Zatorska, A. Zatorski, W. G. Bornmann and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1999, **121**, 11953–11963.
5 C. S. López, C. Pérez-Balado, P. Rodríguez-Grana and A. R. Lera, *Org. Lett.*, 2008, **10**, 77–80.
6 D. Crich and A. Banerjee, *Acc. Chem. Res.*, 2007, **40**, 151–161.
7 V. R. Espejo, X. B. Li and J. D. Rainier, *J. Am. Chem. Soc.*, 2010, **132**, 8282–8284.
8 (*a*) M. Bruncko, D. Crich and R. Samy, *J. Org. Chem.*, 1994, **59**, 5543–5549; (*b*) J. A. González-Vera, M. T. García-López and R. Herranz, *J. Org. Chem.*, 2007, **72**, 5395–5398.
9 W. Yu, Y. Mei, Y. Kang, Z. Hua and Z. Jin, *Org. Lett.*, 2004, **6**, 3217–3219.
10 R. S. Lott, V. S. Chauhan and C. H. Stammer, *J. Chem. Soc., Chem. Commun.*, 1979, 495–496.
11 P. Ventosa-Andrés, J. A. González-Vera, A. M. Valdivielso, M. T. García-López and R. Herranz, *Bioorg. Med. Chem.*, 2008, **16**, 9313–9322.
12 (*a*) S. Takano, M. Moriya, Y. Iwabuchi and K. Ogasawara, *Chem. Lett.*, 1990, 109–112; (*b*) C. Mukai, T. Yoshida, M. Sorimachi and A. Odani, *Org. Lett.*, 2006, **8**, 83–86.
13 (*a*) K. A. Carpenter, G. Weltrowska, B. C. Wilkes, R. Schmidt and P. W. Schiller, *J. Am. Chem. Soc.*, 1994, **116**, 8450–8458; (*b*) R. Krishnamoorthy, L. D. Vazquez-Serrano, J. A. Turk, J. A. Kowalski, A. G. Benson, N. T. Breaux and M. A. Lipton, *J. Am. Chem. Soc.*, 2006, **128**, 15392–15393.

