Natural Product Synthesis

International Edition: DOI: 10.1002/anie.201702530
German Edition: DOI: 10.1002/ange.201702530

Total Synthesis of (−)-Albocycline

*Vijay K. Chatare and Rodrigo B. Andrade**

Dedicated to Professor Franklin Davis on the occasion of his 78th birthday

Abstract: *The macrolactone natural product (−)-albocycline is a promising antibiotic candidate for the treatment of both methicillin resistant Staphylococcus aureus (MRSA) and vancomycin-resistant strains. Herein we report a concise total synthesis of (−)-albocycline in 14 steps from commercially available methyl (R)-3-hydroxybutyrate. Novel key steps include the highly regio- and stereoselective reactions of chiral N-sulfinyl metallodienamines (NSMDs) with aldehydes and the Davis oxaziridine, in addition to the Horner–Wadsworth–Emmons olefination of N-sulfinyl imines.*

Natural products, which account for two-thirds of our antibacterial pharmacopeia, are structurally complex targets for total synthesis.[1] The threat of bacterial resistance and its attendant toll on public health have led to a renaissance in natural product-based antibiotic discovery.[2] In 2013, Tomoda reported that (−)-albocycline (**1**) inhibited methicillin-resistant *Staphylococcus aureus* (MRSA) as potently as vancomycin, an antibiotic of last resort (Figure 1).[3]

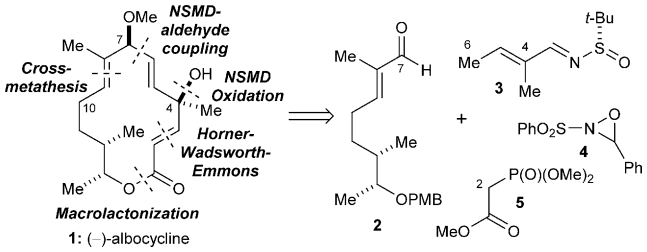


Figure 1. Retrosynthetic analysis of (−)-albocycline (**1**).

Albocycline was isolated by the Tanabe Seiyaku Company in 1967 and Upjohn (as ingramycin) in 1968 from *Streptomyces* strains.[4] The correct structure and absolute stereochemistry of **1** was not established until 1983 by X-ray crystallography.[5] The potent antibacterial activity and architectural complexity manifest in albocycline, which includes a 14-membered macrolactone, four stereogenic centers (two of which are doubly allylic), and three (*E*)-alkenes (one of which is trisubstituted), motivated us to develop a concise chemical synthesis thereof.

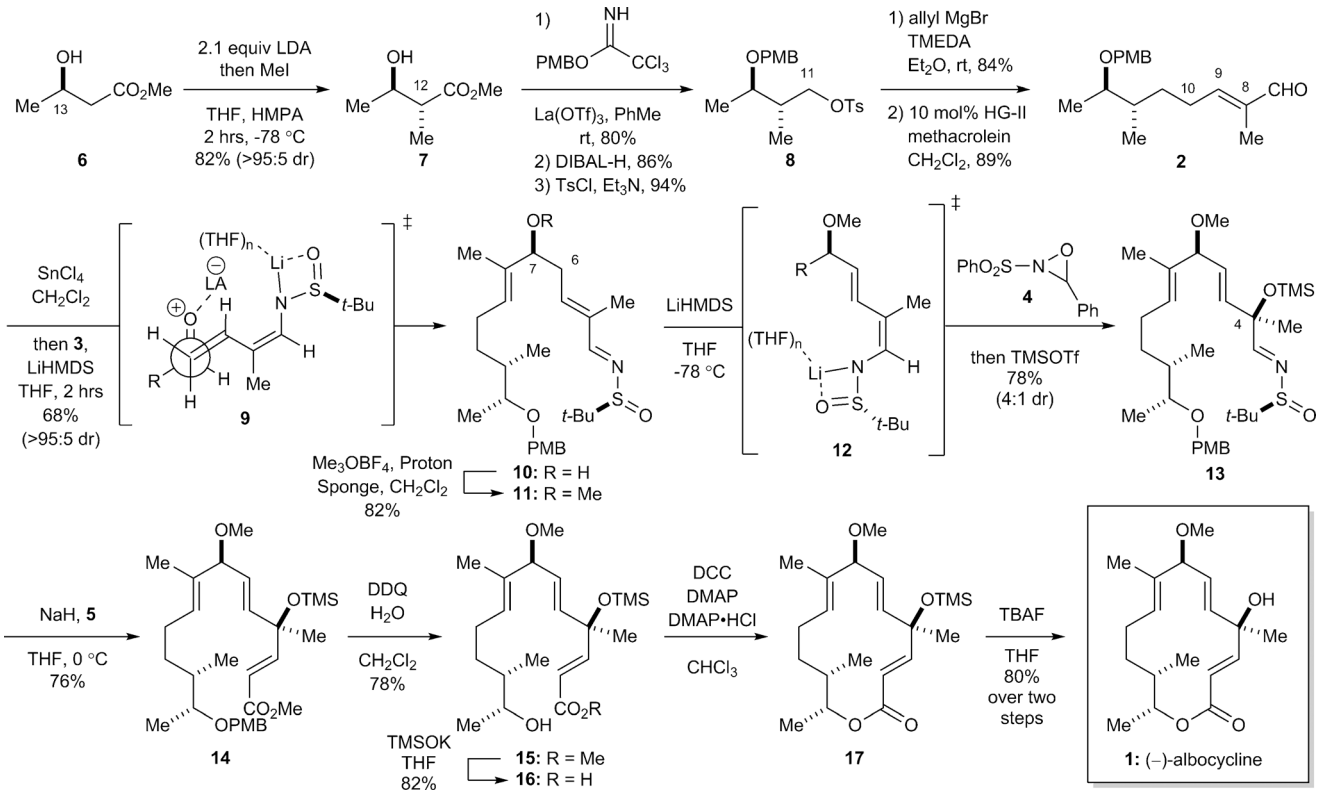
[*] V. K. Chatare, Prof. Dr. R. B. Andrade
Department of Chemistry, Temple University
1901 N. 13thSt., Philadelphia, PA 19122 (USA)
E-mail: randrade@temple.edu
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/anie.201702530.

In 1987, Tanner and Somfai reported the first and only total synthesis of albocycline (i.e., ingramycin) in 40 total steps (21 in the longest linear sequence).[6] To execute a concise total synthesis of **1**, we required a convergent approach and asymmetric methodology capable of accessing and coupling the requisite fragments.[7] In 2013, we reported that chiral, 2,3-indole fused *N*-sulfinyl metallodienamines (NSMDs) efficiently engage acrylates to afford cycloadducts that were elaborated into *Aspdiosperma* alkaloids.[8] We reasoned that under the appropriate reaction conditions, acyclic and ambident NSMDs could both regio- and stereoselectively engage various electrophiles to expedite the total synthesis of **1**.

Retrosynthetically, we envisioned (−)-albocycline (**1**) could be assembled from left-hand C7–C13 fragment **2**, *N*-(*S*)-*tert*-butanesulfinylimine **3**, and trimethyl phosphonoacetate (**4**) (Figure 1). Keck macrolactonization of an appropriately protected seco acid, a tactic used by Tanner and Somfai in their synthesis of **1**, would access the 14-membered ring.[6,9]

Ellman elegantly showed that *N*-sulfinyl metalloenamines, derived from the metalation of enolizable *N*-sulfinyl imines,[10] efficiently add to electrophilic olefins in a 1,4-fashion[11] and aldehydes in a 1,2-fashion.[12] Accordingly, we hypothesized a vinylogous variant (i.e., NSMD derived from **3**) could react at its C6 terminus with the C7 aldehyde of **2** in a regio- and stereoselective manner to convergently prepare the C7 carbinol in **1**. Subsequent metalation and reaction with the Davis oxaziridine (**4**)[13] could serve to regio- and stereoselectively access the tertiary carbinol at C4. Horner–Wadsworth–Emmons olefination would stereoselectively deliver the (*E*)-enoate precursor to the requisite seco acid.

The total synthesis of (−)-albocycline (**1**) began with the preparation of left-hand fragment **2** (Scheme 1). To this end, commercially available (*R*)-methyl 3-hydroxybutyrate (**6**) was subjected to a stereoselective Fráter alkylation (>2 equiv LDA, MeI in THF/HMPA) to furnish *anti*-aldol **7** in 82% yield (>95:5 d.r.) and establish C12 and C13 stereocenters.[14] Protection of the alcohol as its *p*-methoxybenzyl (PMB) ether using PMB trichloroacetimidate and catalytic $La(OTf)_3$ proceeded in 80% yield.[15] Ester reduction with DIBAL-H and tosylation of the resulting primary alcohol with TsCl and Et_3N afforded **8** in 81% yield over two steps. After screening a variety of Cu-catalyzed cross-coupling reactions of allylmagnesium halides with tosylate **8**, we discovered copper salts were not required and the use of TMEDA and allylmagnesium bromide in diethyl ether delivered the desired product in 84% yield.[16] Cross-metathesis of the intermediary terminal olefin with methacrolein (5 equiv) and 10 mol% of the Hoveyda–Grubbs 2nd generation catalyst (HG-II) delivered left-hand fragment **2** in a satisfactory 89% yield on multigram scale.[17]



Scheme 1. Total synthesis of (−)-albocycline (**1**).

With left-hand fragment **2** in hand, we turned our attention to accessing the right-hand C1–C6 portion. We had demonstrated that the reactions of 2,3-indole fused *N*-sulfinyl metallodienamines and acrylates afford cycloadducts that proceed via closed, 6-membered transition states.[8] In order to effect the regioselective coupling between the *N*-sulfinyl metallodienamine derived from **3** (i.e., at C6) and left-hand fragment **2** (i.e., at aldehydic C7), we required the reaction proceed via an open transition state to avoid the undesired cycloaddition (i.e., domino Michael–Mannich) pathway.[8] Of relevance to this task was the elegant work of Kobayashi, who showed $TiCl_4$-promoted Mukaiyama aldol reactions of vinylketene silyl *N,O*-acetals bearing the Evans oxazolidinone auxiliary with aldehydes proceed with high levels of remote 1,7-asymmetric induction.[18] After screening various Lewis acids [e.g., $BF_3{\cdot}OEt_2$, $TiCl_4$, $Ti(OEt)_4$, $La(OTf)_3$], we found that the precomplexation of aldehyde **2** with $SnCl_4$ and subsequent addition of the *N*-sulfinyl lithiodienamine derived from **3** and LiHMDS smoothly furnished carbinol **10** in 68% yield (d.r. > 95:5). We rationalize the exquisite remote 1,7-asymmetric induction of this process by invoking synclinal transition state **9** wherein nonbonded interactions are minimized (Scheme 1).[18,19] The diastereofacial selectivity of the *N*-sulfinyl lithiodienamine is presumably derived from the chelation of the Lewis basic sulfinyl oxygen with THF-solvated lithium, consistent with stereochemical models posited by both Davis and Ellman.[20]

Elaboration of the C3–C13 framework of albocycline (**1**) required the regio- and stereoselective installation of oxygen at C4. As previously discussed, we hypothesized this tactic could be realized by reacting *N*-sulfinyl metallodienamine **12** with the Davis oxaziridine (**4**). Thus, we first methylated the C7 hydroxy using Me_3OBF_4 and Proton Sponge to furnish **11** in 82% yield. Metalation with LiHMDS gave **12**, which was reacted sequentially with oxaziridine **4** then TMSOTf to deliver *N*-sulfinyl imine **13** in 78% yield (d.r. = 4:1) as an inseparable mixture of diastereomers by ^{1}H NMR. Significantly, no elimination of the C7 methoxy group through a possible E1cb pathway was observed. We rationalize the stereochemical course of this process by drawing analogy to the fragment coupling reaction used to access **10**. Specifically, preorganization of the *N*-sulfinyl lithiodienamine serves to sterically block the *Si*-face and favor approach of the Davis reagent (**4**) from the *Re*-face. At this point, we cannot rule out the participation of lithium in directing **4** through coordination with either Lewis basic sulfonyl or oxaziridine oxygen. The highly regioselective nature of this reaction (i.e., α- over γ-attack with **4**) parallels that of lithium dienolates.[21] We are currently in the process of fully investigating the scope and mechanism of these novel reactions of NSMDs.

Endgame for the synthesis of **1** required 1) two-carbon homologation; 2) macrocylization; and 3) protecting group removal. We envisioned the first task could be accomplished by stepwise hydrolysis of the *N*-sulfinyl imine in **13** to expose the aldehyde, followed by a standard olefination protocol. However, consideration of the electrophilicity of the *N*-sulfinyl moiety presented a more efficient and direct alternative. Tian had shown that *N*-sulfonyl imines react with unstabilized Wittig reagents to afford *Z* alkenes in analogy with the classic Wittig reaction of aldehydes.[22] Despite its diminished reactivity, we reasoned the *N*-sulfinyl imine in **13** could react with a suitably nucleophilic olefinating reagent. In

our hands, the stabilized Wittig reagent $MeO_2C(H)C{=}PPh_3$ failed to give any product. Alternatively, the more reactive phosphonate anion derived from **5** and NaH (i.e., the Horner–Wadsworth–Emmons reaction) proved to be a competent and stereoselective olefinating agent. In the event, we obtained **14** in 76% yield as a single stereoisomer.

With the full carbon framework of albocycline (**1**) in hand, we proceeded to access the 14-membered ring. Preliminary macrocyclization experiments using Yamaguchi conditions[23] on seco acid intermediates bearing a free C4-hydroxy resulted in undesired butenolide formation, presumably arising from intermediary C2–C3 $E \rightarrow Z$ olefin isomerization catalyzed by DMAP.[24] Thus, recourse to protecting the carbinol with a TMS group was made (i.e., **13**). Oxidative removal of the C13 *O*-PMB ether in **14** with DDQ furnished **15** in 78% yield. After surveying a number of conditions for the saponification of methyl ester **15**, we found that TMSOK in THF satisfactorily provided seco acid **16** in 82% yield.[25] Keck macrocyclization of **16** was realized with DCC, DMAP and DMAP·HCl as reported by Tanner and Somfai, thus delivering macrolactone **17**.[6] Removal of the C6 *O*-TMS ether with TBAF proceeded without incident, furnishing **1** in 80% yield over two steps. Spectral data (^{1}H and ^{13}C NMR, IR), optical rotation, and R_f values were in full agreement with those reported by Tanner and Okuda.[4,6]

In summary, we have completed a concise total synthesis of (−)-albocycline (**1**) in 14 total steps from commercial methyl (*R*)-3-hydroxybutyrate, which was previously synthesized in 40 total steps (21 in the longest linear sequence). Novel chemistry enabling our synthesis includes the highly regio- and stereoselective reactions of chiral *N*-sulfinyl metallodienamines with aldehydes for C–C bond formation and the Davis oxaziridine for α-hydroxylation. In addition, the first example of the Horner–Wadsworth–Emmons (HWE) olefination of *N*-sulfinyl imines is described. We believe these new methods will find general utility in the synthesis of complex molecules.

Acknowledgements

The NSF (CHE-1362461) and Temple University supported this research. We thank Richard Pederson (Materia) for catalyst support and Harsh Patel for preparing synthetic intermediates.

Conflict of interest

The authors declare no conflict of interest.

Keywords: albocycline · antibiotics · *N*-sulfinyl metallodienamine · total synthesis

[1] a) D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2012**, *75*, 311–335; b) D. J. Newman, G. M. Cragg, *Future Med. Chem.* **2009**, *1*, 1415–1427.
[2] a) C. Walsh, *Nat. Rev. Microbiol.* **2003**, *1*, 65–70; b) K. Lewis, *Nat. Rev. Drug Discovery* **2013**, *12*, 371–387; c) R. Laxminarayan, A. Duse, C. Wattal, A. K. M. Zaidi, H. F. L. Wertheim, N. Sumpradit, E. Vlieghe, G. L. Hara, I. M. Gould, H. Goossens, C. Greko, A. D. So, M. Bigdeli, G. Tomson, W. Woodhouse, E. Ombaka, A. Q. Peralta, F. N. Qamar, F. Mir, S. Kariuki, Z. A. Bhutta, A. Coates, R. Bergstrom, G. D. Wright, E. D. Brown, O. Cars, *Lancet Infect. Dis.* **2013**, *13*, 1057–1098; d) K. Bush, P. Courvalin, G. Dantas, J. Davies, B. Eisenstein, P. Huovinen, G. A. Jacoby, R. Kishony, B. N. Kreiswirth, E. Kutter, S. A. Lerner, S. Levy, K. Lewis, O. Lomovskaya, J. H. Miller, S. Mobashery, L. J. V. Piddock, S. Projan, C. M. Thomas, A. Tomasz, P. M. Tulkens, T. R. Walsh, J. D. Watson, J. Witkowski, W. Witte, G. Wright, P. Yeh, H. I. Zgurskaya, *Nat. Rev. Microbiol.* **2011**, *9*, 894–896.
[3] N. Koyama, M. Yotsumoto, H. Onaka, H. Tomoda, *J. Antibiot.* **2013**, *66*, 303–304.
[4] N. Nagahama, M. Suzuki, S. Awataguc, T. Okuda, *J. Antibiot.* **1967**, *20*, 261–266.
[5] a) A. Furusaki, T. Matsumoto, K. Harada, M. Suzuki, K. Kinoshita, M. Hayashi, K. Nakatsu, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3042–3046; b) R. C. Thomas, C. G. Chidester, *J. Antibiot.* **1982**, *35*, 1658–1664.
[6] D. Tanner, P. Somfai, *Tetrahedron* **1987**, *43*, 4395–4406.
[7] a) N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 2854–2867; *Angew. Chem.* **2009**, *121*, 2896–2910; b) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40–49.
[8] a) S. Zhao, R. B. Andrade, *J. Am. Chem. Soc.* **2013**, *135*, 13334–13337; b) S. Zhao, R. B. Andrade, *J. Org. Chem.* **2017**, *82*, 521–531.
[9] E. P. Boden, G. E. Keck, *J. Org. Chem.* **1985**, *50*, 2394–2395.
[10] a) M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600–3740; b) P. Zhou, B. C. Chen, F. A. Davis, *Tetrahedron* **2004**, *60*, 8003–8030.
[11] H. M. Peltier, J. A. Ellman, *J. Org. Chem.* **2005**, *70*, 7342–7345.
[12] T. Kochi, T. P. Tang, J. A. Ellman, *J. Am. Chem. Soc.* **2003**, *125*, 11276–11282.
[13] F. A. Davis, R. T. Reddy, W. Han, R. E. Reddy, *Pure Appl. Chem.* **1993**, *65*, 633–640.
[14] G. Fráter, U. Muller, W. Gunther, *Tetrahedron* **1984**, *40*, 1269–1277.
[15] A. N. Rai, A. Basu, *Tetrahedron Lett.* **2003**, *44*, 2267–2269.
[16] Z. M. Ruan, D. Dabideen, M. Blumenstein, D. R. Mootoo, *Tetrahedron* **2000**, *56*, 9203–9211.
[17] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
[18] S. I. Shirokawa, M. Kamiyama, T. Nakamura, M. Okada, A. Nakazaki, S. Hosokawa, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 13604–13605.
[19] M. Kalesse, M. Cordes, G. Symkenberg, H. H. Lu, *Nat. Prod. Rep.* **2014**, *31*, 563–594.
[20] a) F. A. Davis, *J. Org. Chem.* **2006**, *71*, 8993–9003; b) T. P. Tang, J. A. Ellman, *J. Org. Chem.* **1999**, *64*, 12–13.
[21] G. Casiraghi, F. Zanardi, G. Appendino, G. Rassu, *Chem. Rev.* **2000**, *100*, 1929–1972.
[22] D. J. Dong, H. H. Li, S. K. Tian, *J. Am. Chem. Soc.* **2010**, *132*, 5018–5020.
[23] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
[24] T. Takahashi, H. Watanabe, T. Kitahara, *Tetrahedron Lett.* **2003**, *44*, 9219–9222.
[25] E. D. Laganis, B. L. Chenard, *Tetrahedron Lett.* **1984**, *25*, 5831–5834.

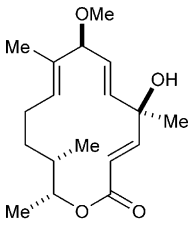
Manuscript received: March 9, 2017
Final Article published: ■■ ■■, ■■■■

Communications

Natural Product Synthesis

V. K. Chatare,
R. B. Andrade* _____ ■■■■–■■■■

Total Synthesis of (−)-Albocycline



(−)-albocycline

An antibiotic candidate: A concise total synthesis of the macrolactone (−)-albocycline in 14 steps from methyl (*R*)-3-hydroxybutyrate is reported. Key steps are the highly regio- and stereoselective reactions of chiral *N*-sulfinyl metallodienamines with aldehydes and the Davis oxaziridine, in addition to the Horner–Wadsworth–Emmons olefination of *N*-sulfinyl imines.

