Aiming for Branimycin: Synthesis of the *cis*-Decalin Core

Valentin S. Enev,* Martina Drescher, Hanspeter Kählig, Johann Mulzer*

Institute of Organic Chemistry, University of Vienna, Währingerstrasse 38, 1090 Vienna, Austria
Fax +43(1)427752189; E-mail: valentin.enev@univie.ac.at; E-mail: johann.mulzer@univie.ac.at

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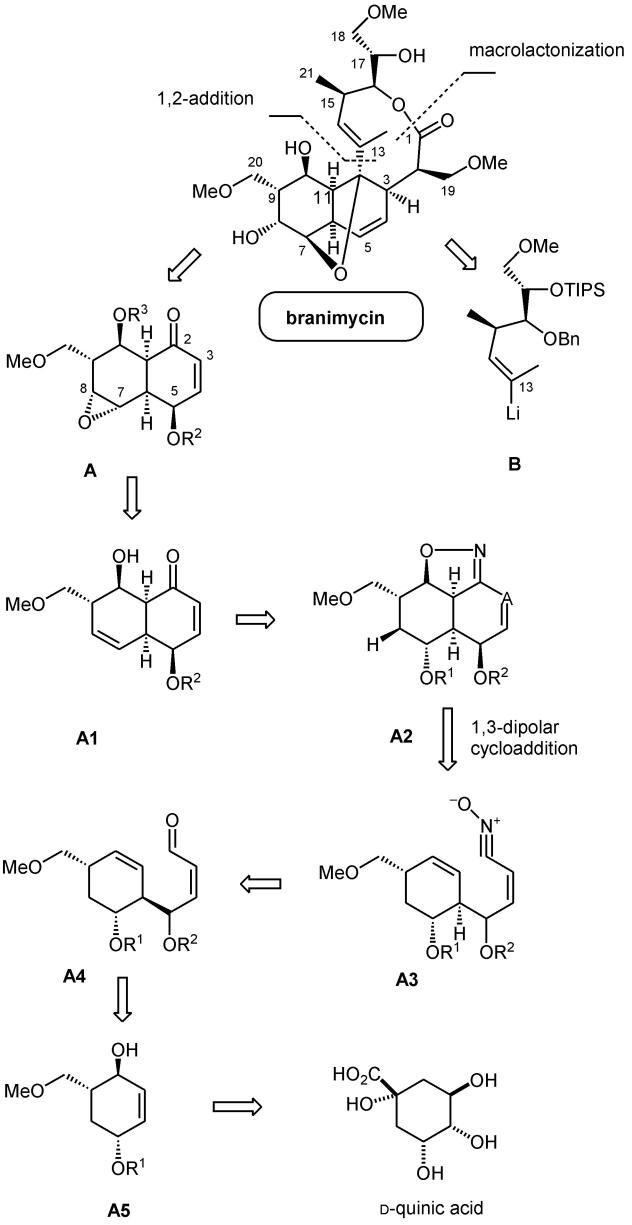
Abstract: Starting from quinic acid, a highly substituted, *cis*-α,β unsaturated nitrile oxide was synthesiszed and involved in a 1,3-dipolar cycloaddition to afford a precursor of the *cis*-decalin system of branimycin.

Key words: branimycin, 1,3-dipolar cycloaddition, *cis*-α,β-unsaturated oximes, quinic acid

The increasing resistance of bacterial pathogens against standard antibiotics combined with an emerging threat of bioterrorism has led to the urgent need for developing innovative anti-infective drugs.[1] A novel family of naturally occurring compounds that show activity against pathogenic microbes has been isolated in the early 1980s by workers at Pfizer and Upjohn: the nargenicins and nodusmycin.[2] Some years later the related compound coloradocin was described.[3] Recently, branimycin, an unusual member of this family has been isolated and structurally characterized by the Laatsch group in Göttingen.[4] First biological tests have shown that branimycin is highly active against *Streptomyces viridochromogenes*. The structure of branimycin, including the unusual configuration at C17, has been reliably elucidated by multidimensional ^{1}H NMR and ^{13}C NMR experiments.[4] These antibiotics are of potential interest as they combine low toxicity with a broad spectrum of high antibacterial activities combined with considerable oral availability. Additionally, the complex highly oxygenated *cis*-fused decalin core, the 1,4-oxygen bridge and the macrolide ring present considerable challenge for total synthesis.

Our retrosynthetic strategy for the synthesis of branimycin, illustrated in Scheme 1, suggests the disconnection into the highly substituted *cis*-decalin moiety **A** and vinyllithium subunit **B**[5] – which will be coupled at a late stage via 1,2-addition under concomitant epoxide opening and formation of the C2–C7-oxygen bridge. The C3-appendage could then be installed via a Claisen rearrangement of the C3-allylic alcohol. In this letter a model study is reported which aims for the construction of a highly oxygenated enantiomerically and diastereomerically pure *cis*-decalin system.



Scheme 1

Quinic acid seemed a reasonable starting material for the synthesis of the core fragment **A**, expecting that the existing chiral centers could control the construction of the remaining stereogenic centers. The key step in our approach is the intramolecular nitrile oxide olefin cycloaddition (INOC) of intermediate **A3** to afford oxazolidine **A2**, which in turn should be cleaved to β-hydroxy ketone **A1**. The C7–C8 double bond in **A1** was to be formed via an E_2-elimination from an 8-OMs derivative.

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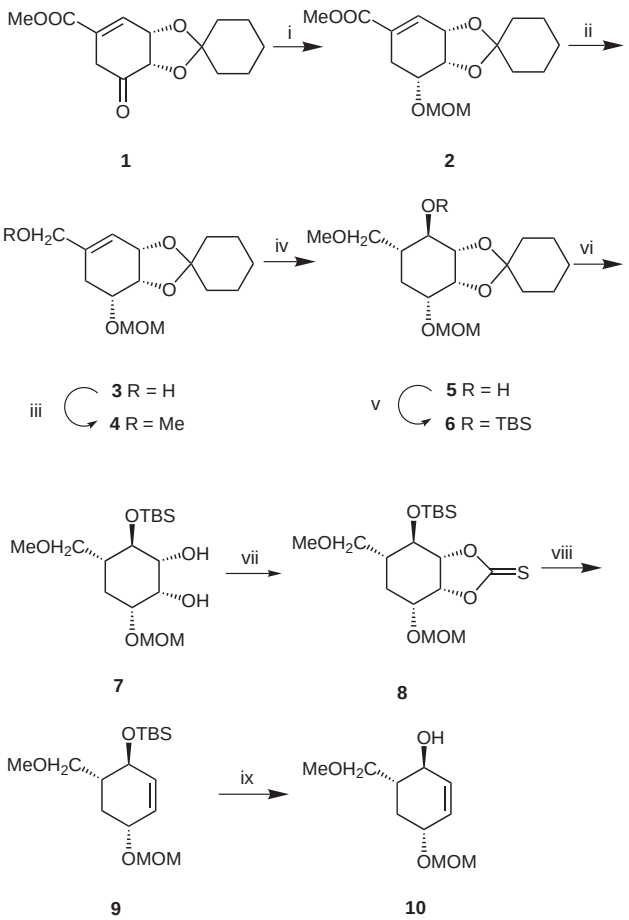
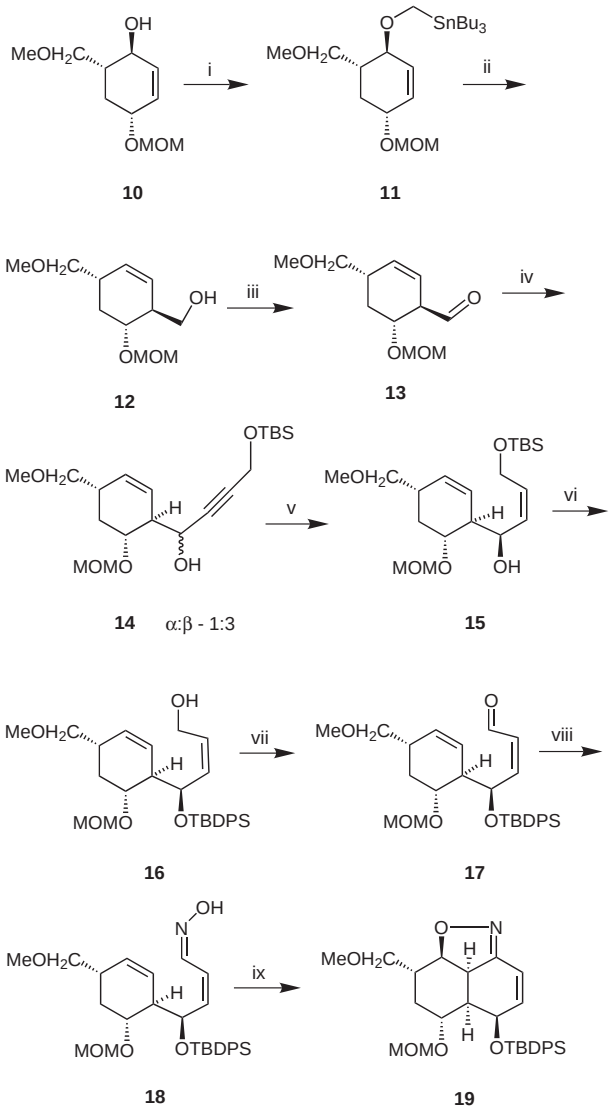
As the most challenging step in this sequence we recognized the synthesis of *cis*-α,β-unsaturated nitrile oxide **A3** from aldehyde **A4**.

We started from the known ketone **1**,[6] which after reduction and MOM protection gave ester **2** in 89% yield. Reduction of **2** and methylation of the resulting alcohol afforded **4** in 87% yield. Hydroboration of **4** followed by oxidative work up,[7] furnished alcohol **5** as a single isomer in excellent yield, which was subsequently protected as TBS ether **6**. The cyclohexylidene ketal **6** was transformed to the olefin **9**, according to the Corey–Hopkins protocol.[8] Compound **9** was then deprotected to give the allylic alcohol **10** (Scheme 2). Wittig–Still rearrangement of **10**, followed by Dess–Martin oxidation produced aldehyde **13** as a single isomer in good overall yield. Treatment of aldehyde **13** with the lithium salt of TBS protected propargyl alcohol afforded **14** as a 1:3 mixture of α- and β-alcohols which were easily separated to give the desired **14β** epimer. The absolute stereochemistry of **14β** was assigned by NMR spectra of the corresponding Mosher esters. Reduction of **14β** with Lindlar catalyst, protection of the secondary alcohol as a TBDPS ether and deprotection of the primary OH group afforded compound **16** in 54% yield over 3 steps. Finally, Dess–Martin oxidation of alcohol **16** gave α,β-unsaturated aldehyde **17**. After intensive experimentation we found that in presence of molecular sieves (4 Å) and three equivalents of polymer-supported di-*tert*-butyl pyridine as a base, aldehyde **17** reacts with hydroxylamine hydrochloride to isomerically pure *cis*-α,β-unsaturated oxime **18** in 80% yield (Scheme 3).

To the best of our knowledge this is the first example for a stereoselective synthesis of a *cis* α,β-unsaturated oxime.



Scheme 2 *Reagents and conditions*: i) $NaBH_4$–MeOH, then MOM-Cl, Hünig's base 89%; ii) DIBAL, –78 °C, 92%; iii) MeI, NaH, THF–DMF, 87%; iv) $BH_3{\cdot}SMe_2$, –20 °C then $NaBO_3{\cdot}4H_2O$, THF, 92%; v) TBSCl, imidazole, DMF, 90%; vi) TsOH, MeOH, r.t., 90%; vii) $Im_2C{=}S$, Tol, reflux, 5 h, 82%; viii) 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidene, 90%; ix) TBAF, THF, r.t., 92%.



Scheme 3 *Reagents and conditions*: i) Bu_3SnCH_2I, KH, THF, r.t., 90%; ii) BuLi, –78 °C to –40 °C, 62%; iii) Dess–Martin oxidation, 90%, iv) Li-$CCCH_2OTBS$, THF, –78 °C, 60%; v) H_2/Lindlar cat. 62%; vi) TBDPSCl, imidazole, THF, then TsOH, 90%; vii) Dess–Martin oxidation; viii) $NH_2OH{\cdot}HCl$, di-*tert*-butyl pyridine polymer bound, 4 Å MS, THF, 40 °C, 12 h, 80%; ix) *t*-BuOCl, CH_2Cl_2, –40 °C, 2 h then pyridine, 12 h, 64%.

Finally, treatment of compound **18** with one equivalent of *t*-BuOCl at –40 °C[9] followed by pyridine at room temperature afforded the desired *cis*-isoxazoline **19** in a 64% yield.[10] The stereochemistry of **19** was confirmed by NOESY experiments.[11]

In conclusion, we have demonstrated that quinic acid could be a suitable starting material toward the *cis*-decalin core of branimycin. Further investigations on the synthesis of branimycin are currently under way in our laboratories.

Acknowledgment

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References

(1) (a) *Antibiotic Resistance: Origin, Evolution, Selection and Spread*; Chadwick, D. J.; Goode, J., Eds.; Wiley: Chichester, **1997**. (b) Levy, S. B. *Sci. Ann.* **1998**, *278*, 32; and cited literature.

(2) Review: (a) Kallmerten, J. *Studies in Natural Products Chemistry*, Vol. 17; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, **1995**, 283–310; and cited literature.
(b) Nargenicin: Celmer, W. D.; Chmurny, C. N.; Moppett, C. E.; Ware, R. S.; Watts, P. C.; Whipple, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 4203. (c) See also: Tone, J.; Shibakawa, R.; Maeda, H.; Yamauchi, Y.; Niki, K.; Saito, M.; Tsukuda, K.; Whipple, E. B.; Watts, P. C.; Moppett, C. E.; Jefferson, M. T.; Huang, L. H.; Cullen, W. P.; Celmer, W. D. *20th Interscience Conf. Antimicr. Agents and Chemoth.* New Orleans, LA, Abstract 62, Sep. 22-24, **1980**.
(d) Nodusmycin: Whaley, H. A.; Chidester, C. G.; Mizak, S. A.; Wnuk, R. J. *Tetrahedron Lett.* **1980**, 3659. (e) See further: Whaley, H. A.; Coates, J. H. *21st Interscience Conference on Antimicrobial Agents and Chemotherapeutics*, Chicago, IL, Abstract 187, Nov. 4-6, **1981**.

(3) (a) Jackson, M.; Karwowski, J. P.; Theriault, R. J.; Fernandes, P. B.; Semio, R. C.; Kohl, W. H. *J. Antibiot.* **1987**, *40*, 1375. (b) Rasmussen, R. R.; Scherr, M. H.; Whittern, D. N.; Buko, A. M.; McAlpine, J. B. *J. Antibiot.* **1987**, *40*, 1383.

(4) Speitling, M.; Grün-Wollny, I.; Hannske, F. G.; Laatsch, H. *12 and 13 IRSEER Naturstofftage der DECHEMA e.V. Irsee* **2000**, **2001**, poster sessions.

(5) Rosenbeiger, D. *Diploma Thesis*; Universität Wien, **2004**; *International ASCMC Symposium*, Abstract P160, Moscow, May, **2004**.

(6) Ketone **6** is easily available in a five-step sequence from quinic acid see: Ulibarri, G.; Nadler, W.; Skrydstrup, T.; Audrain, H.; Chiaroni, A.; Riche, C.; Grierson, D. *J. Org. Chem.* **1995**, *60*, 2753.

(7) Kabalka, G.; Shoup, T.; Goudgaon, M. *J. Org. Chem.* **1989**, *54*, 5930.

(8) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 1979.

(9) Stevens, R. V.; Beaulieu, N.; Chan, W.; Daniewski, A. R.; Takeda, T.; Waldner, A.; Williard, P. G.; Zutter, U. *J. Am. Chem. Soc.* **1986**, *108*, 1039.

(10) **Selected Data.**
Compound **18**: IR (neat): 3344, 2947, 1613, 1514, 1463, 1376, 1249 cm^{-1}. ^1H NMR (600 MHz): δ = 7.62 (2 H, d, *J* = 7.7 Hz), 7.59 (2 H, d, *J* = 8Hz), 7.53 (1 H, dd, *J* = 10.5, 0.9 Hz) 7.46–7.32 (6 H, m), 7.27 (1 H, br s), 6.04 (1 H, ddd, *J* = 11.3, 9.1, 0.9 Hz), 5.79 (1 H, ddd, *J* = 11.4, 10.6, 1,2), 5.77 (2 H, m), 4.88 (1 H, ddd, *J* = 9.2, 2.1, 1.2 Hz), 4.41 (1 H, d, *J* = 7.0 Hz), 4.30 (1 H, d, *J* = 7Hz), 3.69 (1 H, ddd, *J* = 11.6, 8.7, 3.7 Hz), 3.36 (3 H, s), 3.31 (1 H, dd, *J* = 8.8, 6.4 Hz), 3.28 (1 H, dd, *J* = 8.9, 6.6 Hz), 3.24 (3 H, s), 2.50 (1 H, m), 2.21 (1 H, m), 2.15 (1 H, m), 1.32 (1 H, ddd, *J* = 12.3, 11.7, 11.7 Hz), 1.01 (9 H, s). ^{13}C NMR (150 MHz): δ = 147.3 (CH), 139.8 (CH), 136.0 (CH), 135.9 (CH), 133.9 (C), 133.3 (C), 129.2 (CH), 129.7 (CH), 129.6 (CH), 127.6 (CH), 127.5 (CH), 125.6 (CH), 121.0 (CH), 96.4 (CH_2), 76.8 (CH_2), 75.8 (CH), 68.6 (CH), 58.9 (CH_3), 55.4 (CH_3), 51.3 (CH), 36.4 (CH), 32.8 (CH_2), 26.9 (CH_3), 19.5 (C). HRMS: *m/z* calcd for $C_{30}H_{41}NO_5Si$: 523.2754; found: 523.2778.
Compound **19**: IR (neat): 1922, 1560, 1456, 1377, 1197, 1122, 1072 cm^{-1}. ^1H NMR (600 MHz): δ = 7.75 (2 H, d, *J* = 6.8 Hz), 7.69 (2 H, d, *J* = 8.0 Hz), 7.50–7.30 (6 H, m), 6.30 (1 H, dd, *J* = 10.1, 2.8 Hz), 6.10 (1 H, ddd, *J* = 10.1, 1.5, 1.5 Hz), 4.83 (1 H, d, *J* = 6.9 Hz), 4.62 (1 H, d, *J* = 6.9 Hz), 4.60 (1 H, m), 4.41 (1 H, dd, *J* = 8.7, 8.7 Hz), 3.64 (1 H, ddd, *J* = 10.4, 10.4, 3.6 Hz), 3.47 (1 H, dd, *J* = 9.4, 4.7 Hz), 3.37 (1 H, dd, *J* = 9.4, 3.6 Hz), 3.10 (1 H, dd, *J* = 8.2, 5.8 Hz), 3.40 (3 H, s), 3.34 (3 H, s), 2.51 (1 H, m), 1.91 (1 H, ddd, *J* = 13.4, 3.7, 3.7 Hz), 1.66 (1 H, m), 1.35 (1 H, ddd, *J* = 13.4, 13.4, 10.9 Hz), 1.09 (9 H, s). ^{13}C NMR (150 MHz): δ = 155.4 (C), 143.4 (CH), 136.0 (CH), 135,9 (CH), 133.1 (C), 127.8 (CH), 127.6 (CH), 129.9 (CH), 120.0 (CH), 117.0 (CH), 97.6 (CH2), 78.2 (CH), 73.5 (CH), 73.4 (CH_2), 73.1 (CH), 59.2 (CH_3), 55.7 (CH_3), 48.6 (CH), 44.2 (CH), 38.1 (CH), 33.0 (CH_2), 27.1 (CH_3), 19.1 (C). HRMS: *m/z* calcd for $C_{30}H_{39}NO_5Si$: 523.2598; found: 521.2584.

(11) Selected NOE data for **19** is shown in Figure 1.

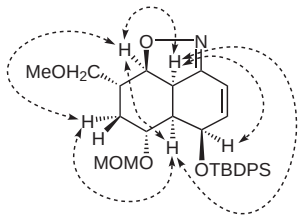

Figure 1