Synthesis of the Tetracyclic Core of the Neomangicols Using a Late-Stage Indene Alkylation

Jessica L. Wood, Brian G. Pujanauski, and Richmond Sarpong*

Department of Chemistry, University of California, Berkeley, California 94720 rsarpong@berkeley.edu

Received May 8, 2009

ABSTRACT



A general approach to the tetracyclic core of the neomangicol natural products via a late-stage indene alkylation reaction is presented. This strategy sets the stage for access to the neomangicol family and, in addition, provides a potential biogenetically inspired entry to the mangicol natural products.

Historically, the carbon framework of terpenoid natural products has proven to be a synthetic challenge due to the lack of functional groups on these molecules that can direct C-C bond formation.¹ As a result, synthetic chemists must design strategies for terpenoid syntheses that maximize carbon-carbon bond formation. Enolate methodology has been featured prominently in a wide range of C-C bond forming cyclization tactics (e.g., intramolecular aldol and Dieckmann reactions) en route to terpene natural products, which often necessitate the removal of the enolate carbonyl oxygen at a late stage. In the context of [5, 6] bicyclic ringcontaining terpene natural products, we envisioned that indenes, which possess acidities comparable to carbonyl compounds (e.g., ketones), could serve as enolate equivalents in late-stage bond-forming events. In this communication, we present the application of this tactic to the synthesis of the tetracyclic core of the natural product neomangicol C (2, Figure 1).

Neomangicol C is a member of a group of rearranged sesterterpenoids isolated from a marine fungus of the genus



Figure 1. Selected neomangicol and mangicol natural products.

Fusarium, which possess varied bioactivity.² For example, neomangicols A and B (1a and 1b, Figure 1) have shown in vitro cytotoxicity against human colon carcinoma.

Furthermore, neomangicol B (1b) has shown potency against the Gram-positive bacterium *Bacillus subtilis* similar

⁽¹⁾ For a recent discussion on terpene synthesis, see: Hudlicky, T.; Reed, J. *The Way of Synthesis: Evolution of Design and Methods for Natural Products Synthesis*, 1st ed.; Wiley-VCH: Weinheim, 2007; pp 207–215.

⁽²⁾ Renner, M. K.; Jensen, P. R.; Fenical, W. J. Org. Chem. 1998, 63, 8346–8354.

to that of the aminoglycoside gentamycin and may prove to be of general utility as an antibiotic.² Preliminary studies have not identified significant bioactivity for neomangicol C (2), and there is evidence that suggests it may be an isolation artifact arising from the net loss of HCl or HBr from 1a or 1b, respectively.²

To date, there have been no reports of synthetic work toward the neomangicols. However, studies by Uemura³ and Paquette⁴ have recently begun to address the synthesis of the related mangicols⁵ (e.g., mangicol A (**3**) and B (**4**), Figure 1). Mangicol A is of interest as a unique structural motif that possesses anti-inflammatory activity.

A series of feeding studies has demonstrated that the neomangicols may arise from a rearrangement of the mangicol skeleton (see $\mathbf{B} \rightarrow \mathbf{A}$, Figure 1).⁵ We envisioned that our model studies on the neomangicols would offer an opportunity to test the reverse of the biosynthetic proposal by employing a semipinacol/Wagner-Meerwein⁶ ring contraction (see $\mathbf{A} \rightarrow \mathbf{B}$, Figure 1) to construct the mangicol skeleton.

Despite their relatively small size, the neomangicols and mangicols possess several challenging features from a synthetic standpoint. For example, these natural product families possess nine and eleven stereocenters, respectively. Additionally, the vinyl halide moiety present in neomangicols A and B is highly unusual in sesterterpene natural products. Our initial studies have focused on the neomangicols and specifically the tetracyclic core of neomangicol C. This presents an opportunity to investigate the potential application of indene alkylation chemistry to the synthesis of these highly complex rearranged sesterterpenoids. Importantly, the core of neomangicol C will serve as a starting point for the synthesis of neomangicols A and B, as well as the mangicols.

Our retrosynthetic analysis of 2 (Scheme 1) features a latestage disconnection to indene 5, which offers a potential





solution to the construction of terpenoid frameworks that incorporate a fused [5, 6] bicyclic ring system. An appealing

(4) (a) Pichlmair, S.; de Lera Ruiz, M.; Basu, K.; Paquette, L. A. *Tetrahedron* **2006**, *62*, 5178–5194. (b) Pichlmair, S.; de Lera Ruiz, M.; Vilotijevic, I.; Paquette, L. A. *Tetrahedron* **2006**, *62*, 5791–5802.

aspect of our approach was that the indene cyclization precursor 5 could be readily constructed in a convergent manner from vinyl triflate 6 and boronic ester 7.

Our synthetic studies commenced with the preparation of boronic ester 7 as illustrated in Scheme 2. The sequence





began with Knoevenagel condensation of 2-bromo-5-methoxybenzaldehyde (8)⁷ and the sodium salt of Meldrum's acid (9), which provided adduct 10 in 85% yield.⁸ Of note, numerous attempts to effect the Knoevenagel condensation using the conditions of Fillion (cat. pyrrolidinium acetate),⁹ which work well for electron-rich aryl aldehydes, resulted in lower yields. A conjugate reduction of alkylidene 10 was effected with sodium triacetoxyborohydride (STAB), and the resulting Meldrum's acid derivative was methylated under standard conditions (K₂CO₃, MeI). At this stage, a formal Friedel–Crafts acylation using polyphosphoric acid (PPA) proceeded with concomitant loss of acetone and carbon dioxide to yield indanone 11 in 80% yield over the three steps.¹⁰

Reduction of indanone **11** upon treatment with DIBAL-H gave an inconsequential diastereomeric mixture (3:1 dr) of indanol products,¹¹ which was immediately protected to afford MOM ether **12**. Installation of the boronic ester moiety was accomplished via halogen-metal exchange with *t*-BuLi at -78 °C followed by a quench of the resulting aryl anion with dioxaborolane **13** to give **7** in 93% yield. The overall sequence for the preparation of boronic ester **7** can be routinely performed on gram scale.

Having established reliable access to 7, we turned our attention to the preparation of vinyl triflate 6 (eq 1). This

⁽¹⁰⁾ The success of the Friedel-Crafts reaction using PPA was significant, given that earlier attempts with Lewis acids such as $Sc(OTf)_3$ returned carboxylic acid i whereas AlCl₃ did effect cyclization, but also led to the cleavage of the methyl ether to yield ii.



(11) Reduction also proceeded efficiently with Li(Ot-Bu)₃AlH, NaBH₄, and LiEt₃BH with equal but opposite diastereocontrol.

⁽³⁾ Araki, K.; Saito, K.; Arimoto, H.; Uemura, D. Angew. Chem., Int. Ed. 2004, 43, 81-84.

⁽⁵⁾ Renner, M. K.; Jensen, P. R.; Fenical, W. J. Org. Chem. 2000, 65, 4843-4852.

⁽⁶⁾ For a review, see: Hanson, J. R. Wagner-Meerwein Rearrangements. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 705–719.

⁽⁷⁾ Tietze, L. F.; Brasche, G.; Grube, A.; Böhnke, N.; Stadler, C. Chem.-Eur. J. 2007, 13, 8543-8563.

⁽⁸⁾ Margaretha, P.; Polansky, O. E. Tetrahedron Lett. 1969, 57, 4983–4986.

⁽⁹⁾ Dumas, A. M.; Seed, A.; Zorzitto, A. K.; Fillion, E. *Tetrahedron Lett.* **2007**, *48*, 7072–7074.

compound was available in short order by enolate formation and triflation starting from easily obtained β -ketoester **13**.¹² Of note, **13** can be prepared in highly enantioenriched form,¹³ which presents an avenue for the enantioselective synthesis of these natural products.



Subsequent screening revealed an optimal set of conditions for the Suzuki cross-coupling of **6** with boronic ester **7** (Scheme 3; 10 mol % PdCl₂(PPh₃)₂, 1:1 *i*-PrOH/2 M



aq. Na₂CO₃), which afforded **14** in 80% yield.¹⁴ At this juncture, two-stage reduction of the ethyl ester moiety followed by elimination of the MOM ether using pyridinium *p*-toluenesulfonate (PPTS) gave indene conjugate **15**. Attempted removal of the MOM ether group using other protic conditions (e.g., KHSO₄ in PhMe at >60 °C) resulted in formation of a tetrasubstituted double bond (see **18** \rightarrow **19**, Scheme 4), presumably via the mechanism



as shown. Oxidation of the primary hydroxyl group of 15

(Scheme 3) set the stage for the key indenide anionmediated C-C bond formation to forge the tetracyclic core of neomangicol C.

Deprotonation of indenes and subsequent reactions of the resulting anions have been studied in great detail.¹⁵ In line with literature precedent, we investigated a range of bases such as *t*-BuLi, KO*t*-Bu and the amide base LiTMP (see Table 1, entries 1-3, respectively) to effect deprotonation

Table 1. Optimization of the Tetracyclization Step^a

entry	conditions	time	result
1	<i>t</i> -BuLi (16 equiv) THF, -78 °C	15 min	SM + decomp.
2	KOt-Bu (6 equiv) MeOH, 23 to 50 °C	12 h	Indene isomerization + decomp.
3	LiTMP (3 equiv) THF, -78 to 23 °C	5 h	Indene isomerization
4	Triton B (8 equiv) DMSO, 23 °C	2 min	50% yield of 16 + byproducts
5^b	Triton B (1 equiv) DMF, -42 °C	10 min	60% yield of 16 + byproducts
$6^{b,c}$	Triton B (1 equiv) DMF, -60 °C	40 min	92% yield of 17

^{*a*} Standard protocol involved addition a solution of Triton B in methanol to a solution of **5** in the indicated solvent (0.04 M). ^{*b*} Reverse addition of the substrate (**5**) to a solution of the Triton B was used. ^{*c*} Yield was determined following oxidation of the crude product (**16**) with Dess–Martin periodinane.

of indene 5. The use of *t*-BuLi was ineffective and returned starting material along with significant decomposition (entry 1). Both KO*t*-Bu and LiTMP led to isomerization of the indene double bond (entries 2-3), suggesting that deprotonation was occurring; however, none of the desired tetracycle was observed.

On the basis of the pioneering studies of Sprinzak, we were drawn to the use of hydroxide bases such as Triton B to effect indene alkylations.¹⁶ Gratifyingly, subjecting indenyl aldehyde **5** to Triton B (8 equiv) in DMSO at rt over 2 min provided a 50% yield of alcohol **16** as a 2:1 mixture of epimers, which could be separated by column chromatography with some difficulty, along with several unidentified byproducts (entry 4).

Encouraged by this initial result, we embarked on optimization studies of the Triton B-mediated cyclization of **5** by varying the solvent, temperature and reaction times. Ultimately, we identified a set of optimal conditions which utilized 1 equiv of Triton B in DMF at -60 °C (entry 6).

The crude allylic alcohol product (16) was oxidized immediately following workup to enone 17, which served

⁽¹²⁾ Barco, A.; Beretti, S.; Pollini, G. P. Synthesis 1973, 316.

^{(13) (}a) Saigo, K.; Koda, H.; Nohira, H. Bull. Chem. Soc. Jpn. 1979, 52, 3119–3120. (b) Ramachandran, P. V.; Chen, G. M.; Brown, H. C. J. Org. Chem. 1996, 61, 95–99.

⁽¹⁴⁾ Initial attempts to prepare adducts related to 14 using a Grignard reagent generated from 12 and addition to β -ketoester 13 gave low returns of the desired product.

^{(15) (}a) Cedheim, L.; Eberson, L. Synthesis 1973, 3, 159. (b) Makosza, M. Tetrahedron Lett. 1966, 38, 4621–4624. For applications in organometallic chemistry, see: (c) Bringtzinger, H. H.; Fischer, D.; Mülhaupt, R.; Rieger, B.; Waymouth, R. M. Angew. Chem., Int. Ed. 1995, 34, 1143–1170. For enantioenriched indenide anions, see: (d) Hoppe, I.; Marsch, M.; Harms, K.; Buchi, G.; Hoppe, D. Angew. Chem., Int. Ed. 1995, 34, 2158–2160.

^{(16) (}a) Ghera, E.; Sprinzak, Y. J. Am. Chem. Soc. 1960, 82, 4945–4952.
(b) Avramoff, M.; Sprinzak, Y. J. Am. Chem. Soc. 1960, 82, 4953–4955.

to significantly simplify ¹H and ¹³C NMR analysis. This compound possesses functional handles in the A and B rings that make it an attractive precursor to the neomangicol natural products.¹⁷

In summary, we report the first synthesis of the tetracyclic core of the neomangicols via an efficient indene alkylation strategy. This design provides a starting point for the syntheses of the biosynthetically related neomangicol and mangicol natural products by utilizing a powerful alternative to enolate chemistry in the synthesis of this subset of

Me CO_EL Me Several conditions

(18) Birman, V. B.; Zhao, Z.; Guo, L. Org. Lett. 2007, 9, 1223–1225.

terpenes. Current efforts are focused on advancing 17 to neomangicols A-C.

Acknowledgment. We are grateful to UC Berkeley, the NIH (NIGMS RO1 GM84906-01), and the American Cancer Society (RSG-09-017-01-CDD) for generous financial support. B.G.P. thanks the CA•TRDRP for a Thesis Fellowship Award. We are indebted to Eric Simmons (UC Berkeley) for discussions and suggestions. R.S. is a 2009 Alfred P. Sloan Foundation Fellow and a 2009 Camille Dreyfus Teacher-Scholar.

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9010008

⁽¹⁷⁾ Initial attempts to prepare tetracycle **17** from indene ester **iii** by employing the optimized conditions for the cyclization of **5**, or the conditions of Birman, ¹⁸ resulted in the recovery of **iii** or the corresponding indene double-bond isomer.