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Synthesis of an anthracyclinone bearing an unprecedented aromatic ring-fused bridgehead-hydroxylated bicyclo[3.1.1]heptanol

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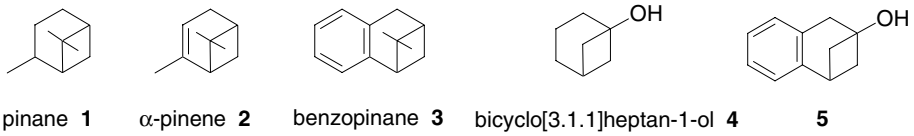
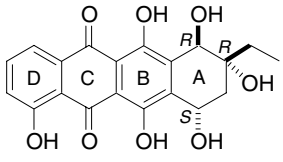
Abstract—This Letter describes the unexpected stereospecific formation of a novel anthracyclinone incorporating the unprecedented aromatic ring-fused bridgehead-hydroxylated bicyclo[3.1.1]heptanol scaffold.

The bicyclo[3.1.1]heptane ring system is a common structural element found in numerous monoterpene and sesquiterpene natural products. For instance, pinane skeleton **1**, containing a bicyclo[3.1.1]heptane ring with a *gem*-dimethyl bridge, is a common constituent of monoterpenes from the wood and leaf oils of many higher plants, particularly Coniferae, as well as some algae and insects.[1] Closely related α-pinene **2** is the most widely distributed monoterpene and is a major component of turpentine oil.[1] Bicyclo[3.1.1]heptanes containing a fused aromatic ring (e.g., benzopinane **3**) are not naturally occurring but reports of their synthesis and properties abound.[2–8] Bicyclo[3.1.1]heptane derivatives functionalized with bridgehead oxygen atoms (e.g., bicyclo[3.1.1]heptan-1-ol **4**) are known constituents of naturally occurring glycosides,[9] as are their unsaturated derivatives containing double bonds within the six-membered ring.[10] To our knowledge, however, bicyclo[3.1.1]-heptanes bearing both a bridgehead-alcohol and a fused aromatic ring (e.g., **5**) are a previously unreported class of compounds.

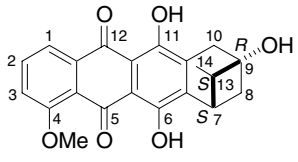
During the course of our synthetic efforts aimed at developing a practical route towards β-rhodomycinone **6** starting from daunomycin·HCl **8a**, we identified an unexpected 4-membered ring closure that provided stereoselective access to anthracyclinone **7**, the prototypical member of an unprecedented class of compounds bearing a bridgehead-hydroxylated bicyclo[3.1.1]heptanol with a fused aromatic ring.



pinane **1** α-pinene **2** benzopinane **3** bicyclo[3.1.1]heptan-1-ol **4** **5**



β-rhodomycinone **6**



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Keywords: Anthracyclinone; Bicyclo[3.1.1]heptanol; Sodium cyanoborohydride; Sulfonylhydrazone.
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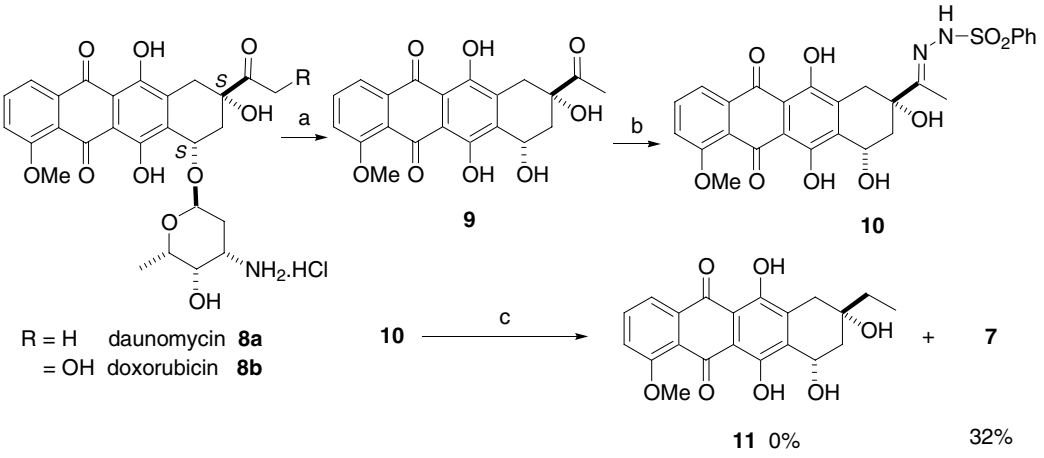
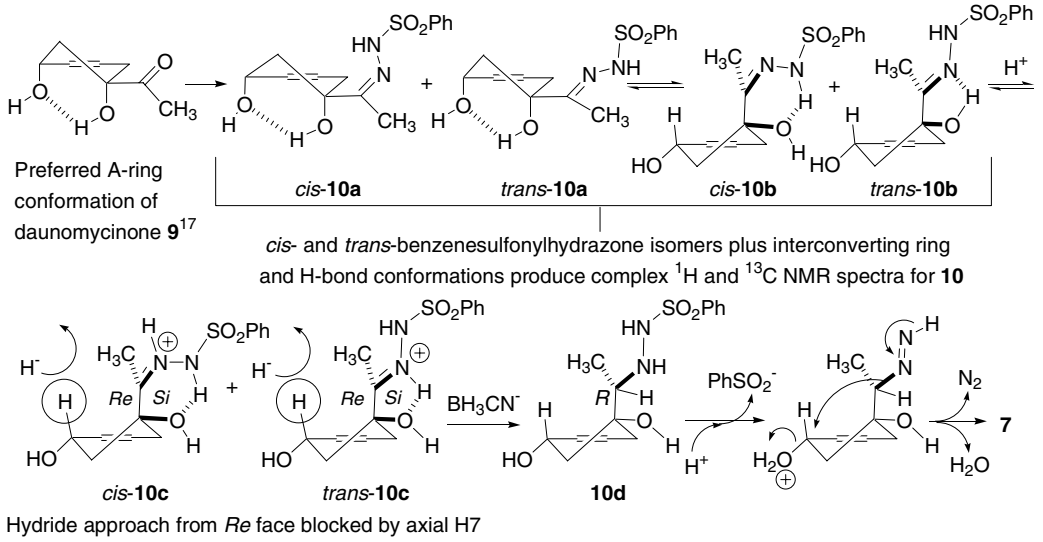
Our proposed route towards β-rhodomycinone **6** involved, (i) acid-catalyzed hydrolysis of the daunosamine sugar from daunomycin·HCl **8a**;[11] (ii) conversion of the aglycone (daunomycinone) **9** to its 13-benzenesulfonylhydrazone **10** followed by reduction to give 13-deoxyanthracyclinone **11**;[12] (iii) demethylation of the 4-methoxyl group of **11**,[13] and finally (iv) regio- and stereoselective benzylic hydroxylation at C10 with trimethylamine *N*-oxide[14] to afford **6**.

Deglycosylation of daunomycin **8a** proceeded smoothly under the conditions reported by Yoo and co-workers[11] to afford **9** in 89% yield (lit. 98%). Walsh and Olson[12] recently disclosed a method for preparing 13-deoxyanthracyclines wherein anthracycline 13-keto groups were converted into 13-arylsulfonylhydrazones, which were subsequently reduced under acidic conditions with $NaCNBH_3$ to the requisite methylene compounds. The 13-arylsulfonylhydrazones of doxorubicin **8b** were obtained in good yields by reaction with various *p*-substituted (i.e., *p*-CH_3, *p*-Cl, *p*-F, *p*-NO_2) benzenesulfonylhydrazines in anhydrous methanol. For the aglycone daunomycinone **9**, we found that conversion into its 13-benzenesulfonylhydrazone **10** was, for solubility reasons, best carried out in anhydrous THF, wherein its reaction with benzenesulfonylhydrazine was quantitative (single spot by TLC; THF–petroleum spirit 1:1) after overnight stirring at rt (Scheme 1). ^1H and ^{13}C NMR spectra for **10** ($CDCl_3$) were complex and difficult to interpret, being consistent with a mixture of *cis*- and *trans*-benzenesulfonylhydrazones and perhaps different H-bonded conformational isomers (Scheme 2).

Crude benzenesulfonylhydrazone **10** was initially subjected to the reductive conditions reported by Walsh and Olsen[12] (*p*-toluenesulfonic acid (TsOH) or pyridinium *p*-toluenesulfonate (PPTS) with $NaCNBH_3$ in methanol at 60 °C). These reactions consistently provided multiple products by TLC analysis as well as unchanged **10**, and showed no evidence by mass spectrometry



Scheme 1. Reagents and conditions: (a) 0.2 N HCl, 90–95 °C, 89%;[11] (b) NH_2NHSO_2Ph, THF, 18 h, 25 °C, quant.; (c) $NaCNBH_3$, TsOH, DMF, 15 min, 110 °C.



Scheme 2. Proposed mechanism for the stereospecific formation of 7*S*,9*R*,13*S*-**7**.

(EIMS and +ve and −ve ion ESMS) for the formation of the desired product **11** (expected $m/z = 384.1$). ESMS (−ve ion) analysis for the crude reaction mixtures typically displayed a prominent peak at $m/z = 365.2$, corresponding to an M−H species 18 mass units lower than for **11**. Lack of success with Walsh and Olsen's conditions led us to explore the reduction using other combinations of hydride reagents ($NaCNBH_3$, $NaBH_4$ and $NaBH(OAc)_3$), acids (CH_3CO_2H, TsOH and PPTS) and solvents (MeOH, CH_3CO_2H and THF) at various temperatures, however, none of these reactions provided any trace of **11** and similarly showed multiple products and unreacted **10** by TLC analysis, as well as −ve ion ESMS spectra in which a peak at $m/z = 365.2$ (as before) was apparent.

Using Maryanoff's conditions for the reduction of tosylhydrazones to methylenes (i.e., $NaCNBH_3$, TsOH, 1:1 DMF–sulfolane, 110 °C),[15] we noted that (i) **10** was completely consumed within 15 min and that a single new spot of higher R_f than **10** was visible by TLC; (ii) the reaction mixtures prominently displayed the previously observed $m/z = 365.2$ peak in their −ve ion ESMS spectra. After purification by silica gel chromatography and comprehensive 2D-NMR characterization (DQF-COSY, HMQC, HMBC and NOESY), it was clear that the product was not **11** but novel anthracyclinone **7**.

The yields of **7** under these conditions were consistently around 30%, which seemed low considering the clean conversions that were observed from TLC analysis. It was subsequently apparent that the remaining mass corresponded to highly polar (presumably polymerized) material that could only be eluted using MeOH. Attempts to optimize the yield of **7** by varying the reaction conditions met with limited success; although it was determined that sulfolane could be omitted from the reaction without affecting the yield. The 7*S*,9*R*,13*S* absolute stereochemistry for **7** was unambiguously assigned based on the 7*S*,9*S* stereochemistry of its daunomycin precursor and from NOEs (Fig. 1).

The generally accepted mechanism for the reduction of tosylhydrazones to methylenes under acidic conditions invokes an initial hydride attack on the sp^2 carbon of a protonated tosylhydrazonium ion to generate the reduced tosylhydrazine derivative. Elimination of *p*-toluenesulfinic acid from the tosylhydrazine subsequently gives rise to a diazene intermediate, which decomposes by losing N_2 to afford the corresponding methylene compound, Eq. 1.[16]

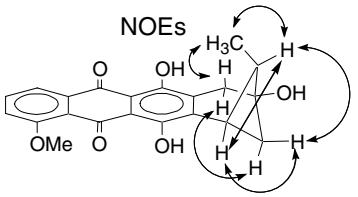


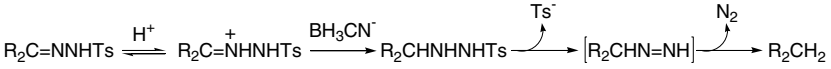
Figure 1. NOEs observed in the NOESY spectrum (500 MHz, 600 ms mixing time) of **7**.

protonate to create a good benzylic leaving group, which loses H_2O following attack by C13 to yield **7**.

Although reasonable, this mechanism is incomplete since it cannot account for the fact that only the 7*S*,9*R*,13*S* stereoisomer of **7** was formed in the reaction. The 7*S*,9*R* stereochemistry would be predicted in **7** from the above mechanism based on the 7*S*,9*S* stereochemistry of daunomycin·HCl **8a** precursor. However, unless hydride reduction of benzenesulfonylhydrazone **10** is stereospecific, with a hydride ion attacking the protonated benzenesulfonylhydrazonium ion from just one face, some of the 7*S*,9*R*,13*R*-epimer of **7** should also be observed.

The A-ring of daunomycinone **9** is known to prefer a conformation in which the two hydroxyl groups at C7 and C9 adopt a pseudo-diaxial orientation stabilized by an intramolecular 6-membered hydrogen bond (H-bond) ring (Scheme 2, **9**).[17] Similar conformations can be envisaged for the *cis*- and *trans*-isomers of benzenesulfonylhydrazone **10** (Scheme 2, *cis*-**10a** and *trans*-**10a**). However, **10** presents additional H-bond donor and acceptor groups in its benzenesulfonylhydrazone moiety, which could potentially compete with the C7–OH for H-bonding to C9–OH by forming 5- and 6-membered H-bond rings. These alternative H-bonded conformers could either retain the pseudo-diaxial orientation of the C7 and C9 alcohols (Scheme 2, not shown) or, alternatively, a ring-flip could occur to reposition the two alcohols in a pseudo-diequatorial orientation (Scheme 2, *cis*-**10b** and *trans*-**10b**). As mentioned previously, ^1H and ^{13}C NMR spectra for **10** were extremely complex supporting the notion that **10** probably exists (in $CDCl_3$) as an equilibrium mixture of a number of these isomers/conformers, which interconvert slowly on the NMR timescale.

Protonation of *cis*-**10b** and *trans*-**10b** under acidic conditions would result in formation of the *cis*- and *trans*-benz-



(1)

An analogous mechanism for the formation of **7** from **10** can be postulated wherein the developing negative charge at C13 resulting from loss of N_2 in the final step does not protonate to yield **11** but instead attacks C7. Under the acidic reaction conditions, the C7–OH could

enesulfonylhydrazonium ions *cis*-**10c** and *trans*-**10c**. Models indicate that the *Re* faces of *cis*-**10c** and *trans*-**10c** are both significantly shielded from approaching nucleophiles by the axial hydrogen at C7. If *cis*-**10c** and *trans*-**10c** represent the predominant species present

in the reaction, facially-selective hydride attack from their respective *Si* faces could produce a stereoselective reduction leading exclusively to sulfonylhydrazine **10d**, bearing *R*-stereochemistry at C13. Spontaneous elimination of $PhSO_2^-$ from **10d** followed by N_2 loss would then furnish 7*S*,9*R*,13*S*-**7** by the mechanism described above.

In addition to providing access to novel anthracyclinone **7**, it seems plausible that reduction of benzenesulfonylhydrazones with $NaCNBH_3$ may represent a more generally useful method for accessing other compounds bearing the aromatic ring-fused bridgehead-hydroxylated bicyclo[3.1.1]heptanol scaffold. These studies are currently in progress and will be reported in due course.

Acknowledgement

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Supplementary data

Experimental procedures for the preparation of compounds **7** and **10** are provided along with full characterization data for **10**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.080.

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