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# Studies on the Synthesis of Landomycin A. Synthesis of the Originally Assigned Structure of the Aglycone, Landomycinone, and Revision of Structure

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The originally proposed structure (**2**) of landomycinone, the aglycone of landomycin A, has been synthesized and shown to be nonidentical to the naturally derived landomycin A aglycone. The synthesis of **2** features the Dötz benzannulation reaction of chromium carbene **5** and alkyne **6**, and the intramolecular Michael-type cyclization reaction of the phenolic naphthoquinone **20**. It is proposed that natural landomycinone possesses the alternative structure **3**, but attempts to access this structure via the Michael-type cyclization of the isomeric phenolic naphthoquinone **38** have been unsuccessful.

## Introduction

Landomycin A[1] is a member of the angucycline antibiotic family, a group that now numbers over 100 members.[2,3] Landomycin A in particular has been studied as a potential antitumor agent.[1,4,5] Although the mode of action of landomycin A has not been established unequivocally, it is known that the natural product interacts with DNA[5] and inhibits DNA synthesis and $G_1$/S cell cycle progression.[6]

Landomycin A possesses a broad spectrum of activity against the National Cancer Institute's panel of 60 cancerous cell lines.[5,7] At 1 $\mu$M, landomycin A is more active than bleomycin, vinblastine, and paclitaxel in inhibition of tumor colony formation in single cell suspensions of freshly obtained human tumor cells.[5] Although the mechanism of action has not been determined at the molecular level, landomycin A is known to inhibit DNA synthesis by stopping cell cycle progression from the $G_0/G_1$ (resting) phase to S (synthesis) phase.[6] We have speculated that the hexasaccharide chain of landomycin A could serve as a DNA binding agent, similar to that of the oligosaccharide portions of the aureolic acids and calicheamycin, which are known to be critical for DNA binding and recognition.[8−11] Supporting this hypothesis

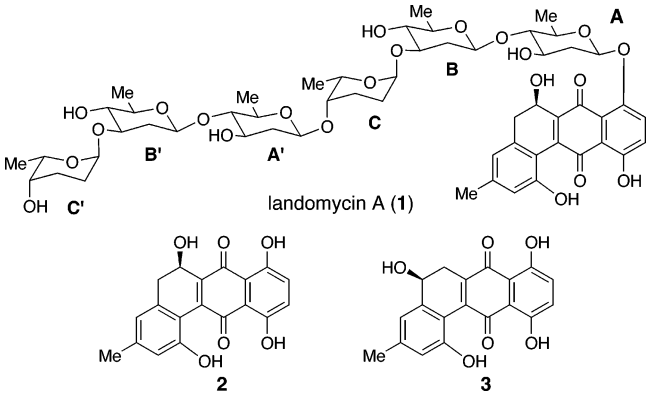


**FIGURE 1.** Structures of landomycin A (**1**) and landomycinone (**2**) proposed by Rohr and the revised structure of landomycinone (**3**).

is knowledge that the cytostatic activities of other members of the landomycin family (e.g., landomycins B−E) depend on the length of the oligosaccharide chain.[4] The initial structural assignment of landomycin A was made by Rohr in 1990[7] and was subsequently revised to the currently accepted structure, **1**.[1] The gross connectivity assignments were made primarily through the use of high-field 2D-NMR analysis, and the absolute configuration of the secondary alcohol was assigned by application of Nakanishi's exciton chirality method.[12]

Despite their interesting biological properties and structural relationship to other members of the angucy-

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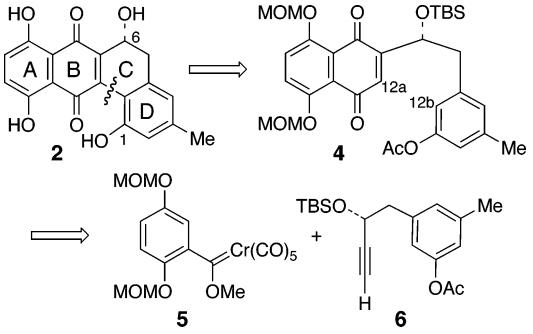



**FIGURE 2.** Retrosynthetic analysis of **2**.

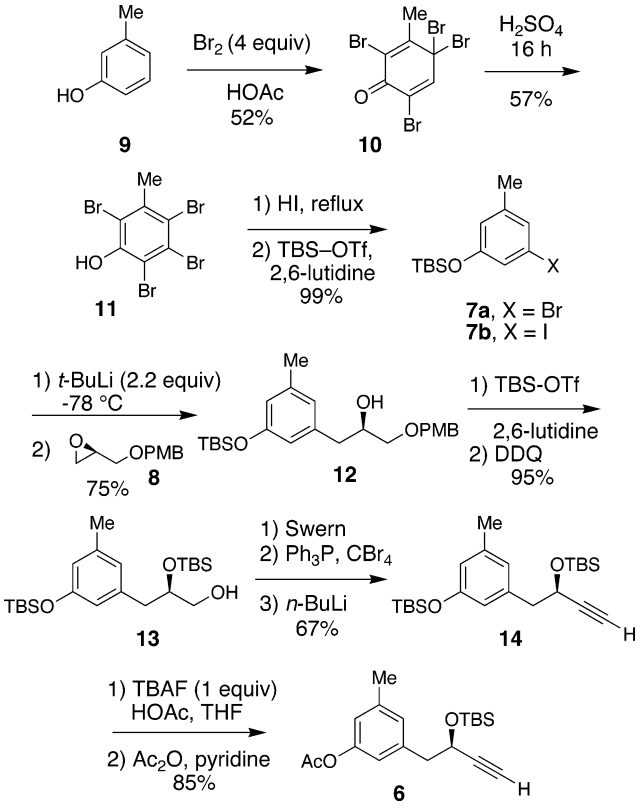
cline group,[2,3] relatively little work has appeared on the synthesis of the landomycins. Syntheses of this hexasaccharide fragment have been completed by the Sulikowski, Yu, and Roush groups,[13−15] but thus far no reports on the synthesis of the landomycine aglycone, landomycinone, have appeared. A flexible total synthesis of landomycin A would allow for the synthesis of analogues that could be key in elucidating the details of both the possible DNA binding properties and global biological activity.

We report herein an enantioselective synthesis of the originally assigned structure (**2**) of the landomycine aglycone, landomycinone, and revise the structure of the aglycone to the structure depicted as **3**.

## Results and Discussion

**Synthesis of Originally Assigned Landomycin Aglycone 2.** Our strategy for the synthesis of the original landomycin aglyone structure **2** called for the C(12a)−C(12b) bond to be constructed by an intramolecular Michael-type addition[16−18] of the phenolate derived from **4** onto C(12a) of the naphthoquinone residue. We anticipated that intermediate **4**, in turn, could be prepared by the Dötz reaction of chromium carbene **5** and acetylene **6**.[19] The synthesis of acetylene **6** involved the coupling of protected bromophenol **7** and glycidol ether **8** as the key step (Scheme 1). Aryl bromide **7** was synthesized following the procedure of Brittain.[20] Thus, two-stage bromination of *m*-cresol in acetic acid provided tetrabromocyclohexadienone **10** in 52% yield. Exposure of this material to concentrated sulfuric acid induced a 1,2-migration of a bromine substituent, thereby providing tetrabromophenol **11**. Reductive removal of the *o*- and *p*-Br substituents by treatment of **11** with aqueous HI at reflux and then protection of the resulting phenol as a TBS ether provided **7a** contaminated with 5−20% (from various runs) of the corresponding aryl iodide **7b**. The yield of the **7a**/**7b** mixture was nearly quantitative. Because the mixture of **7a** and **7b** could not be separated conveniently, the mixture was subjected to lithium−

**SCHEME 1**




halogen exchange (*t*-BuLi, THF, −78 °C), and the resulting aryllithium species was then treated with (*R*)-glycidyl ether **8**.[21] This reaction provided **12** in 64−75% yield. Protection of the secondary alcohol of **12** as a TBS ether and then removal of the PMB ether upon treatment with DDQ[22] provided **13** in excellent yield. Swern oxidation[23] of **13** provided the corresponding aldehyde, which was then elaborated to acetylene **14** by application of the Corey−Fuchs protocol.[24] Finally, selective removal[25] of the phenolic TBS ether by using TBAF (1 equiv) in the presence of acetic acid and then acylation of the phenol provided the targeted alkyne **6**.

Chromium carbene **5** was prepared from 1,4-dihydroquinone bismethoxymethyl ether (**15**) under standard conditions (Scheme 2).[19] Ortho lithiation of **15** by treatment with *t*-BuLi in THF at −78 °C gave the aryllithium species that was then treated with solid $Cr(CO)_6$. The resulting hydroxy carbene was then treated with methyl triflate, which provided carbene **5** in 75% overall yield. The benzannulation reaction of **5** and **6** gave best results when performed in heptane at 55 °C. Under these conditions, the intermediate hydroquinone mono ether (devoid of the arene $Co(CO)_3$ unit) was obtained in 35−40% yield, along with varying amounts of recovered **5**. However, alkyne **6** was completely consumed, and it was not possible to identify any of the other products of this reaction. Numerous attempts to improve the efficiency of this reaction by screening other benzannulation

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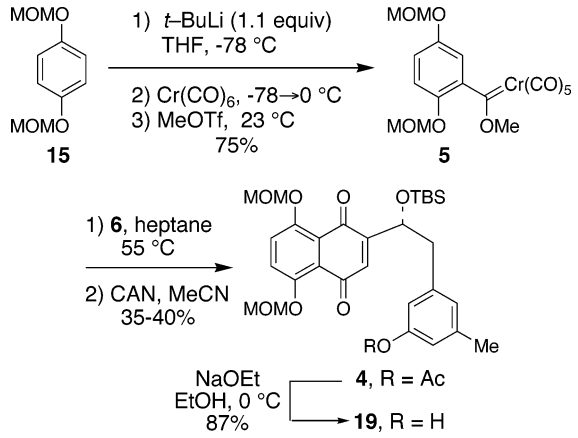
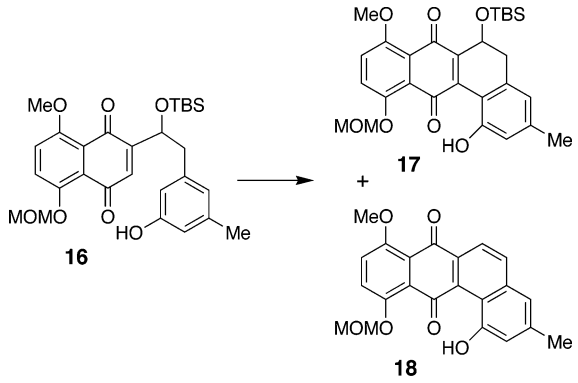
**SCHEME 2**




**SCHEME 3**

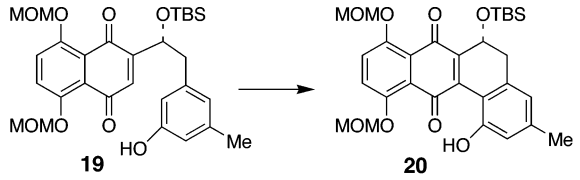



| conditions | T (°C) | results |
|---|---|---|
| $NaHCO_3$, MeOH | 23 | no reaction |
| $Et_3N$, $CH_2Cl_2$ | 23 | decomposition |
| KHMDS, THF | –78 → 23 | no reaction |
| $K_2CO_3$,acetone | 23 → 50 | no reaction |
| $K_2CO_3$, MeOH | 65 | **18**, 26% yield |
| NaOEt, EtOH | 23 → 65 | **17**, 60% yield |

conditions[26–29] using **5** (and related carbenes with different phenol protecting groups as substrates) were not successful. Oxidation of the intermediate hydroquinone mono ether with ceric ammonium nitrate (CAN) then provided the targeted naphthoquinone **4**.

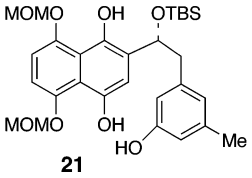
Our plan at the outset was to effect cyclization of phenol deriving from **4** under mildly basic conditions. Initial studies (Scheme 3) were performed by using the phenolic benzoquinone **16** as substrate (deriving from a Dötz benzannulation sequence analogous to the one described above). No reaction was observed when **16** was treated with $NaHCO_3$ in MeOH (23 °C), KHMDS in THF (−78 to 23 °C), or $K_2CO_3$ in acetone (23 to 50 °C), and only products of decomposition were obtained when **16** was treated with $Et_3N$ in $CH_2Cl_2$ at ambient temperature. When **16** was treated with $K_2CO_3$ in MeOH at 65 °C, cyclization was observed, but the only product isolated

**SCHEME 4**




| NaOEt (equiv.) | time (h) | temp. (°C) | solvent | oxidant | result |
|---|---|---|---|---|---|
| 1 | 16 | 55 | $CH_2Cl_2$ | DDQ | no reaction |
| 2 | 16 | 55 | EtOH | HgO | **20** (trace) |
| 2 | 16 | 55 | EtOH | $Ag_2O$ | decomposition |
| 1 | 1 | 65 | EtOH | CAN | decomposition |
| 1 | 1 | 55 | EtOH | $O_2$ (a) | decomposition |
| 0.1 | 24 | 75 | EtOH | $O_2$ (a) | 30% (30% **19**) |
| 0.1 | 16 | 55 | EtOH | benzoquinone | recovered **19**) |
| 0.2 | 60 | 55 | EtOH | air | 42% (6% **19**) |
| 0.1 | 14 | 55 | EtOH | air | 45% (40% **19**) |

(a) $O_2$ was bubbled through the reaction mixture




was **18** deriving from elimination of the C(6)-OTBS unit. However, this elimination reaction was effectively suppressed in a small-scale pilot reaction when **16** was treated with NaOEt in EtOH at 23 °C with warming to 65 °C, which provided the targeted (model) tetracyclic product **17** in 60% yield. Interesting, no deuterium was incorporated when the cyclization of **16** was performed with NaOEt in EtOD, indicating that racemization of the potentially acidic C(6)-H will not occur under these conditions.

On the basis of these results, the decision was made to perform the deacylation and cyclization of **4** in a one-pot sequence. Treatment of **4** with NaOEt in EtOH indeed provided the protected landomycin aglycone **20** in yields up to 60%, but with considerable variability in the yield from run to run. Further examination of the reaction (Scheme 4), by using the purified phenol **19** (generated in 87% yield by treatment of **4** with NaOEt in EtOH at 0 °C) as substrate, revealed that under several sets of conditions, only decomposition of **19** was observed, without any of **20** being obtained. In other instances, a nearly 1:1 mixture of **19** and **20** was obtained (again in variable yield).

Consideration of plausible mechanisms for this Michael-type cyclization indicates that the initial Michael adduct **23** undergoes a series of enolization reactions leading to **26**. An oxidant is required for the final conversion of **26** to naphthoquinone **20**. Because it is known that quinones can oxidize hydroquinones in alkaline solution,[30] it seemed possible that **19** (derived from deacylation of **4**) was serving as the oxidant in this case. Indeed, on several occasions small amounts of dihydronaphthoquinone **21** were obtained from these reactions. Accordingly, efforts were made to identify an alternative, stoichiometric oxidant for use in the cyclization of **19** to **20**. Oxidants such as DDQ, benzoquinone, HgO, or $Ag_2O$ were em-

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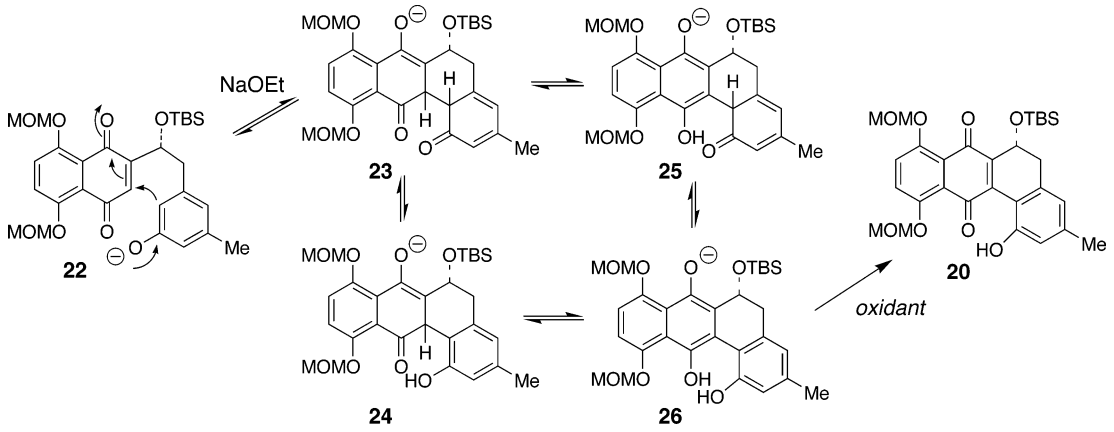
(30) Campbell, T. W. *J. Am. Chem. Soc.* **1951**, *73*, 4190.

**SCHEME 5**




ployed in various reactions of **19** with stoichiometric NaOEt, but no more than trace amounts of **20** was observed under these conditions. Use of $O_2$ as the oxidant similarly gave poor results (only products of decomposition) when stoichiometric NaOEt was used, but 30% of **20** (together with 30% of recovered **19**) was obtained from an experiment in which 0.1 equiv of NaOEt was used under a steady stream of $O_2$. Ultimately, a reproducible set of reaction conditions was developed in which **19** was treated with 0.1 equiv of NaOEt in EtOH (0.05 M) under air, from which the targeted naphthoquinone **20** was obtained in 45% yield along with 40% of recovered **19**, which could be resubjected to the cyclization conditions to obtain additional **20**.

With **20** in hand, we initiated studies on the deprotection sequence that we anticipated would provide synthetic landomycinone, **2** (see Scheme 6). Treatment of **20** with either HCl in ether or $MgBr_2$ in $CH_2Cl_2$ smoothly removed the two phenolic MOM ethers and provided **27** in excellent yield. However, attempted removal of the C(6)-TBS ether from this intermediate using a variety of fluoride sources failed to provide any of **2**; as a general rule, **27** was recovered from these attempted deprotections. Similarly, attempts to remove the TBS ether from **20** by using a variety of fluoride sources were also unsuccessful. However, successful cleavage of the TBS ether was accomplished by treatment of **20** with 0.05 M HCl in MeOH, which provided a ca. 1:1 mixture of **28** and **29**, in which one of the two MOM ethers had been removed,[31] in 85% yield. It is known that landomycinone undergoes dehydration within 1 h when treated with 1 M HCl at 23 °C.[7] It was not surprising, therefore, that a small amount (ca. 5%) of the elimination product **30** was also obtained from the deprotection of **20** in 0.05 M HCl. Finally, treatment of **28** and **29** with $MgBr_2$ (prepared according to Vedejs' procedure)[32] in THF at 0 °C provided synthetic "landomycinone" **2** in 80% yield. A single crystal X-ray structure analysis of the fully deprotected synthetic "landomycinone" verified our structure assignment of the synthetic material as **2**. However, comparison of NMR data for synthetic **2** with published data for the natural landomycinone and with copies of the actual $^1$H NMR spectra provided by Prof. Rohr, indicated that natural

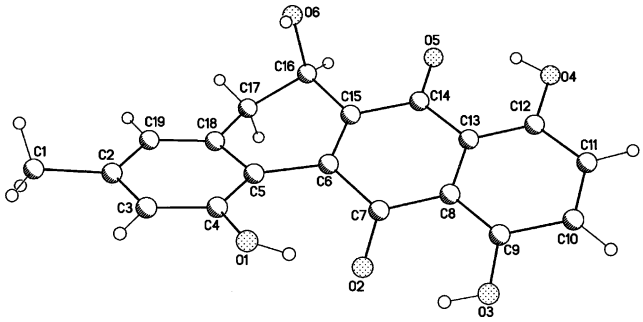
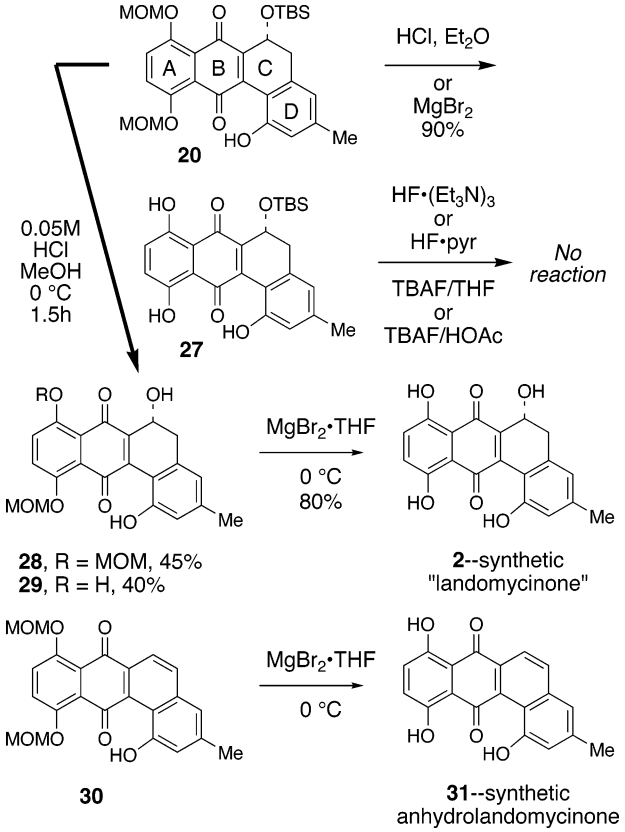



**FIGURE 3.** X-ray crystal structure of synthetic **2**.

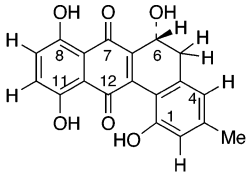
**SCHEME 6**




landomycinone and synthetic **2** are not identical. Among the more striking differences are the chemical shift data for H(2), H(4), H($5_{ax}$), H($5_{eq}$), H(9), and H(10).[1]

(31) The assignment of **29** as the mono-MOM ether deriving from the deprotection of **19** is tentative.

(32) Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702.



| | synthetic 2 $^1$H NMR data (500MHz, $CD_3OD$) | natural landomycinone $^1$H–NMR data (200MHz, $CD_3OD$) |
|---|---|---|
| H (2) | 6.71, s | 6.41, s |
| $CH_3$ (3) | 2.29, s | 2.22, s |
| H (4) | 6.63, s | 6.44, s |
| $H_{ax}$ (5) | 3.00, dd, *J*=15.8, 4.2 Hz | 2.34, dd, *J*=16, 4 Hz |
| $H_{eq}$ (5) | 2.84, dd, *J*=15.8, 3.8 Hz | 2.82, dd, *J*=16, 2 Hz |
| H (6) | 5.15, s | 5.14, s |
| H (9) | 7.28, bs | 6.66, d, *J*= 10 Hz |
| H (10) | 7.28, bs | 6.82, d, *J*= 10 Hz |

| | synthetic 2 | natural landomycinone |
|---|---|---|
| IR ($cm^{-1}$) | 1623, 1589, 1560 | 1705, 1640, 1620, 1588 |
| UV ($\lambda_{max}$, nM) | 495, 287, 258, 222 | 503, 368, 288, 262 |

**FIGURE 4.** Comparison of spectroscopic data for synthetic **2** and natural landomycinone.

The poor solubility of synthetic **2** precluded the collection of a complete set of $^{13}$C NMR data, however the partial $^{13}$C spectrum that we obtained was sufficient to confirm lack of identity of the synthetic and natural materials. Synthetic **2** exhibited resonances at $\delta$ 61.1 and 36.6 for C(5) and C(6), respectively, differing from the $^{13}$C chemical shifts for the previously assigned to C(5) and $^{33}$C(6) the natural aglycone (62.0 and 36.3, respectively).[1]

Analysis of the infrared and ultraviolet spectra of the natural and synthetic material provided further clues as to the structural differences (Figure 4). The carbonyl stretch of the synthetic material at 1623 $cm^{-1}$ is completely consistent with the proposed structure of a doubly hydrogen-bound quinone system, but the 1705 absorption recorded for the natural aglycone[1] is high for even a parent quinone.[33] These data further support the misassignment of the structure of natural landomycinone.

We considered the possibility that the synthetic (**2**) and natural landomycinones might be tautomers, with the quinoide ketones in the A-ring and quinols on the B-ring. The synthetic material was assigned the tautomeric structure assigned for **2** on the basis of bond lengths determined by the X-ray analysis of the synthetic material. The 1.35 and 1.25 Å bond lengths observed for the C−O and C═O bonds, respectively, of synthetic **2** are consistent with standard values for phenol C−O and quinone C═O bond lengths of 1.355 and 1.208 Å.[34] It is unlikely (but not impossible)[33] that the natural material is the other tautomer because of the known propensity of vicinally disubstituted naphthazarins to exist in the tautomer depicted in structure **2**.[35]

To exclude the possibility that synthetic **2** may be a conformational isomer of natural landomycinone, a series of VT-NMR and computational studies were undertaken

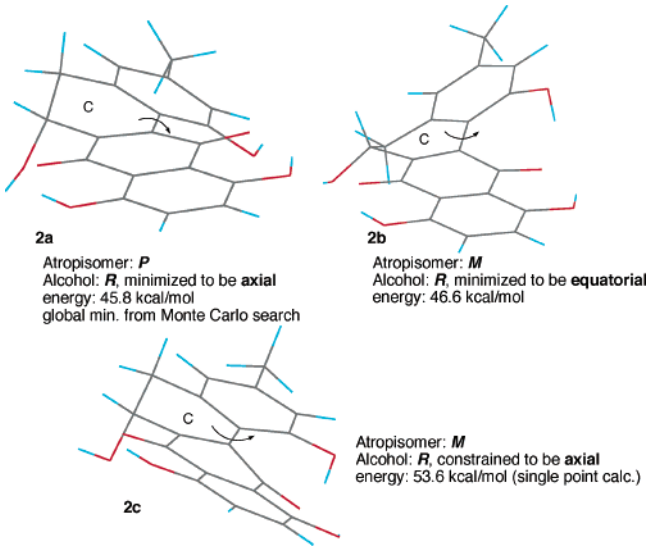


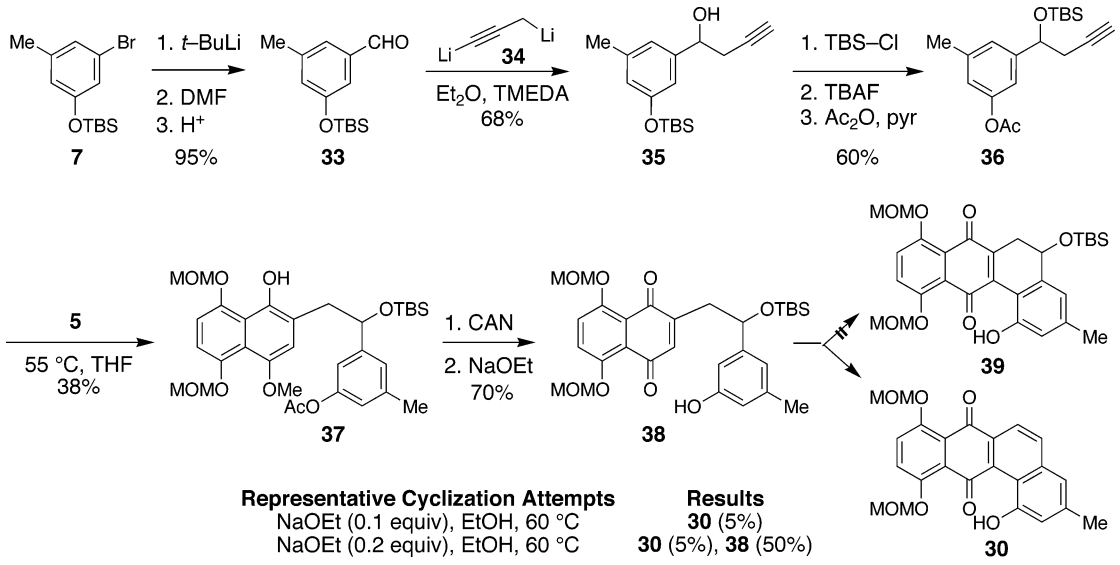

**FIGURE 5.** Minimizations of potential atropisomers of **2**.

(Figure 5). Atropisomerism in fused ring systems is known in the literature (e.g., colchicine).[36] Monte Carlo minimizations of **2** were conducted from a number of different starting points, all of which minimized to conformer **2a,** which has a positive (***P***) twist about the biaryl bond and an axial orientation for the secondary alcohol.[37] The conformer closest in energy with a minus (***M***) twist about the biaryl axis is 0.8 kcal/mol higher in energy. This conformer, **2b**, places the secondary alcohol in the equatorial plane. The computational exclusion of the low energy conformational diastereomer **2b** with an equatorial alcohol is consistent with vicinal coupling constants observed in the $^1$H NMR spectra for both synthetic **2** and natural landomycinone—both of which indicate that the secondary alcohol is axial. None of the low energy conformations detected by the Monte Carlo search had both an ***M*** configuration about the biaryl bond and an axial alcohol. When the alcohol was constrained to adopt such an axial orientation and the dihedral angle of the biaryl linkage was constrained to avoid computational relaxation to the ***P*** atropisomer, the computed energy of **2c** with ***M*** atropisomer stereochemistry is 7.8 kcal/mol higher than that of **2a**. $^1$H NMR spectra of synthetic **2** were measured at temperatures ranging from −20 to 80 °C in order to probe the possibility that other conformations might be accessible, but no significant changes in the NMR spectra were observed.

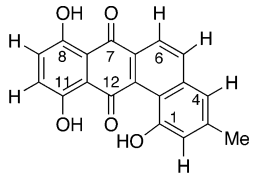
These data indicate that synthetic **2** and natural landomycinone are constitutional and not conformational isomers. Because $^1$H NMR data obtained for synthetic anhydrolandomycinone (**31**), small quantities of which were obtained during the deprotection of **19**, were in excellent agreement with data previously reported for naturally derived anhydrolandomycinone, we propose that the revised structure for natural landomycinone must be **3**, and therefore also that landomycin A must be **32**. Attempts have been made to synthesize **3** by appropriate modifications of our synthesis of **2** (Scheme

(33) Glazunov, V. P.; Tchizhova, A. Y.; Pokhilo, N. D.; Anufriev, V. P.; Elyakov, G. B. *Tetrahedron* **2002**, *58*, 1751.
(34) These bond length data were obtained from Spartan.
(35) Moore, R. E.; Scheuer, P. J. *J. Org. Chem.* **1966**, *31*, 3272.
(36) Wildman, W. C.; Pursey, B. A. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1968; Vol. XI, p 407.
(37) All energies were determined by AM1 calculations (Spartan) after Monte Carlo minimization of the appropriate starting structures.

**SCHEME 7**




7). Thus, treatment of aryl bromide **7** with *t*-BuLi in THF at −78 °C followed by addition of DMF provided aldehyde



| | synthetic 31 $^1$H NMR data (500MHz, $CD_2Cl_2$) | natural anhydrolandomycinone $^1$H–NMR data (200MHz, $CD_2Cl_2$) |
|---|---|---|
| H (1) | 11.06, s | 11.06, s |
| H (2) | 7.36, s | 7.32, d, *J*=2 Hz |
| $CH_3$ (3) | 2.51, s | 2.50, s |
| H (4) | 7.17, s | 7.15, d, *J*=2 Hz |
| H (5) | 8.36, d, *J*=8.8 Hz | 8.34, d, *J*=9 Hz |
| H (6) | 8.21, d, *J*=8.8 Hz | 8.18, d, *J*=9 Hz |
| H (8) | 12.98, s | 12.97, s |
| H (9) | 7.37, d, *J*=9.3 Hz | 7.34, app s |
| H (10) | 7.35, d, *J*=9.3 Hz | 7.34, app s |
| H (11) | 12.49, s | 12.48, s |
| IR ($cm^{-1}$) | 3400, 2960, 2920, 1607, 1584, 1554, 1500 | 3440, 3050, 2960, 2920, 2860, 1610, 1590, 1560, 1500 |

**FIGURE 6.** Comparison of spectroscopic properties of synthetic and natural anhydrolandomycinone (**31**).

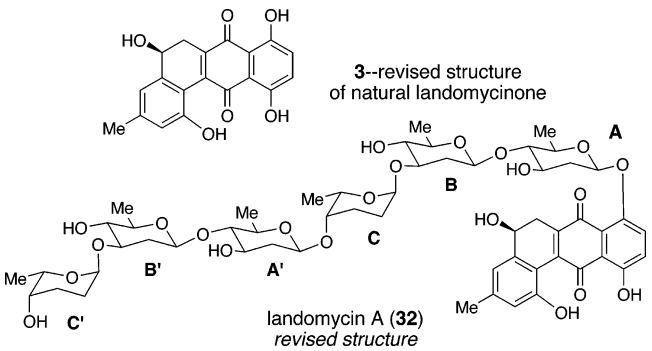



**FIGURE 7.** Revised structures of landomycin A (**32**) and landomycinone (**3**).

**33** in 95% yield following aqueous workup. 1,3-Dilithiopropyne (**34**), generated by treatment of propargyl bromide with 2 equiv of *n*-BuLi, was added to a solution of **33** to provide racemic propargyl alcohol **35**.[38] This secondary alcohol was then protected as the TBS ether. The phenolic TBS ether was then cleaved by treatment of the bis-silylated derivative with TBAF, and the resulting phenol was acylated to give **36**. The Dötz reaction of alkyne **36** and chromium carbene **5** gave hydroquinone product **37** in 38% yield.[19] This reaction proceeded best in THF, in contrast to heptane, which was the best solvent for the Dötz reaction of **5** and **6** discussed previously. Oxidation of hydroquinone **37** to the quinone followed by deprotection of the pendent phenol provided **38** (70% yield), the substrate for the Michael closure. Unfortunately, when phenolic quinone **38** was subjected to the conditions previously used in our synthesis of **19** (vide supra), none of the targeted tetracyclic produce **39** was obtained. Only the elimination product **30** and recovered phenol **38** were obtained. Extensive modification of the reaction temperature, concentration, and base were studied, but without success. In all cases the only product isolated was **30** deriving from cyclization and elimination of the secondary alcohol.

## Summary

The originally proposed structure (**2**) of landomycinone, the aglycone of landomycin A, has been synthesized and shown to be nonidentical to the naturally derived landomycin A aglycone. Our synthesis of **2** features the Dötz benzannulation reaction of chromium carbene **5** and alkyne **6** and the intramolecular Michael-type cyclization reaction of the phenolic naphthoquinone **19**. It is proposed that natural landomycinone possesses the alternative structure **3**, but attempts to access this structure via the Michael-type cyclization of the isomeric phenolic naphthoquinone **38** have been unsuccessful. Therefore, an alternative strategy for synthesis of **3** must be developed in order to verify the structural reassignment of landomycinone and therefore of landomycin A itself.

(38) Cabezas, J. A.; Pereira, A. R.; Amey, A. *Tetrahedron Lett.* **2001**, *42*, 6819.

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

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