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Toward the synthesis of antascomicin B. Synthesis of a model of the C22–C34 fragment via Ireland–Claisen and allylic diazene rearrangements

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ABSTRACT

The C22–C34 fragment of antascomicin B lacking the C31 and C32 hydroxyl groups has been prepared in 11 steps from commercially available 2-hydroxy-cyclohexanone. An Ireland–Claisen rearrangement was employed to install the C26 and C27 stereocenters. Our recently reported diastereoselective acyclic 1,3-reductive transposition was used to establish the remote C23 stereocenter. Directed hydrogenation was employed to set the C29 stereocenter. The model compound contains five of the stereocenters and all of the carbons of the corresponding fragment of antascomicin B.

1. Introduction

The antascomicins are a small family of macrolides that possess sub-nanomolar FKBP12 binding activity, but antagonize the binding of the immunosuppressants rapamycin (Rapamune®) and FK-506 (Prograf®) (Fig. 1).[1] While the antascomicins bind potently to FKBP12, they lack the effector domains of rapamycin or FK-506 that bind to mTOR or calcineurin, respectively. Ley et al. recently reported the first total synthesis of antascomicin B (**1**).[2] Fuwa et al. have published a synthesis of the C18–C34 fragment of antascomicin A.[3] Chakraborty et al. have published syntheses of the C1–C21 and C22–C34 fragments of antascomicin A.[4]

Our proposed total synthesis would entail the preparation of an appropriately protected version of the C22–C34 fragment. Prior to embarking on the total synthesis, we elected to examine the feasibility of our approach using an advanced model system lacking the C31 and C32 hydroxyl groups (Scheme 1). A directed hydrogenation would be used to establish the C29 stereocenter in the later stage of the synthesis. We would make use of our recently reported diastereoselective acyclic 1,3-reductive transposition protocol to install the remote C23 stereocenter.[5] An Ireland–Claisen rearrangement would establish the relative configuration between the C26, C27 and C30 stereocenters.[6]

2. Results and discussion

In our initial approach, we employed 6-hydroxy-2-cyclohexen-1-one (**2**)[7] as our starting material, in spite of the lack of unsaturation at C33–C34 in the natural product (Scheme 2). We had previously found that unsaturated ketones afforded higher diastereoselectivity in the 1,2-addition of carbon nucleophiles to 6-heteroatom substituted cyclohexenones relative to the saturated ketones in some cases (vide infra).[8,9] Similarly, alkynyl nucleophiles exhibited higher diastereoselectivities than their alkenyl counterparts. Thus, addition of propynylMgBr to ketone **2** gave good yield and diastereoselectivity of the desired *anti*-diol **3**. Protection of the 2° hydroxyl group as the TBS ether was followed by semi-hydrogenation of the alkyne to *Z*-alkene **5**. However, we were unable to acylate the resulting hindered 3° alcohol under a variety of conditions.

By contrast, acylation of propargyl alcohol **4** proceeded in high yield (Scheme 3). We found that maximum conversion of alcohol **4** to ester **5** was achieved by concentrating the reaction mixture in vacuo after addition of *n*-BuLi until the reaction mixture became a thick, but stirrable, slurry. Hydrogenation of propargyl ester **7** proceeded in high yield to afford alkene *Z*-**6**, although a 20 mol% catalyst loading and significantly higher H_2 pressure were

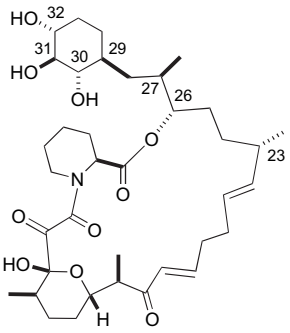

Figure 1. Antascomicin B (**1**).

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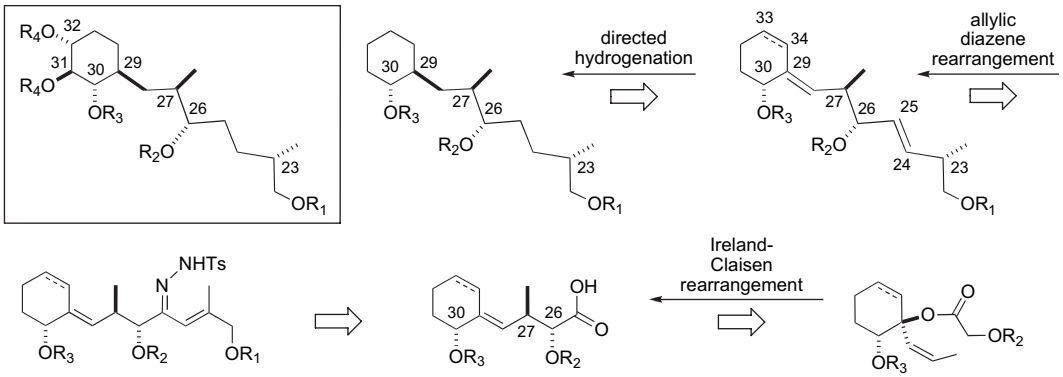
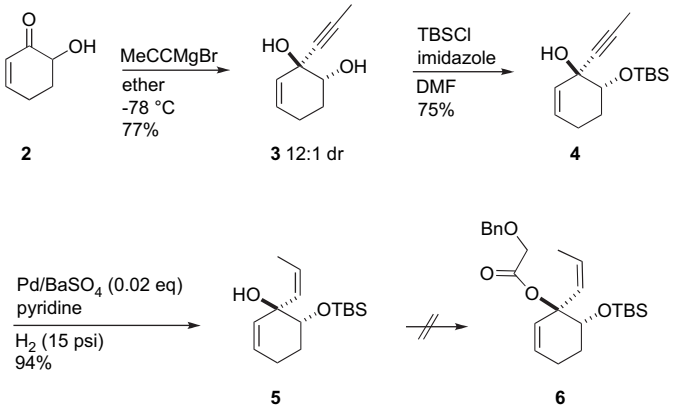


Scheme 1.



Scheme 2.

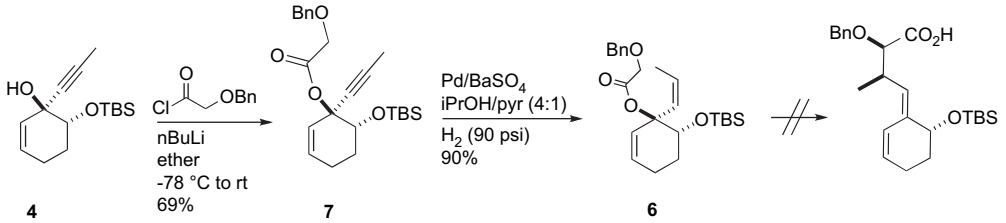
necessary than for the corresponding alcohol.[10] Unfortunately, all attempts under a variety of conditions (e.g., LDA/TMSCl, KHMDS/TIPSOTf) at effecting an Ireland–Claisen rearrangement of ester **6** resulted only in the formation of products resulting from formal 1,3-rearrangements or other decomposition pathways.

The lack of success of the rearrangement of ester **6** was likely due to steric hindrance from the *Z*-methyl substituent on the exocyclic alkene. There are no reported Claisen rearrangements of 3° cyclohexanone or cyclohexenone-derived allylic alcohols in which the exocyclic allylic alkene bears a *Z*-substituent. Indeed, Hart et al. reported a case of an unsuccessful attempt at an exocyclic enolate Claisen rearrangement of a *Z*-substituted cyclic allylic ester.[11] They proposed that the transition state for the Claisen rearrangement suffered from too much allylic strain. It seems likely that ester **6** encountered similar constraints. The doubly allylic nature of the ester in all probability contributed to the undesired reaction pathways, although further investigation would be required to elucidate the details of the reaction outcomes.

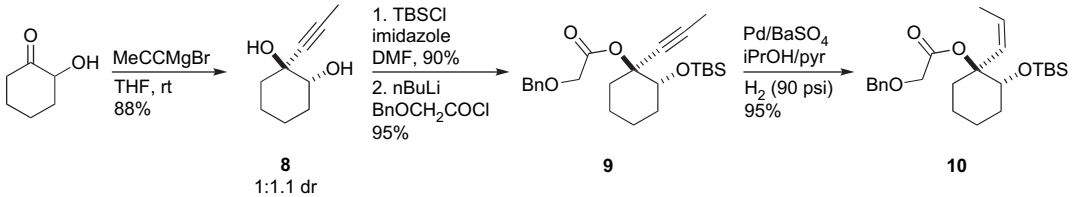
We decided to eliminate the endocyclic alkene in the hopes of avoiding the undesired rearrangement and/or decomposition pathways. To this end, propynylMgBr addition to commercially available 2-hydroxy-cyclohexanone afforded the known *anti*-diol **8**,[9] albeit in an unselective fashion (Scheme 4). Silylation and acylation yielded proparyl glycolate **9**, and hydrogenation as before proceeded in uniformly high yields to give allylic ester **10**.

Ireland–Claisen rearrangement of allylic ester **10** was effected by addition of LTMP to a solution of the ester and TMSCl in THF at −78 °C to give pentenoic acid **11** as a single stereoisomer based on ^{1}H NMR analysis of the crude reaction mixture (Scheme 5). The relative configurations at C26, C27, and C30 were assigned by analogy to extensive earlier studies of the Ireland–Claisen rearrangement of related allylic esters.[6,12] The rearrangement presumably occurred via the conformer shown, in which the larger OTBS-substituted ring carbon was disposed in a pseudo-equatorial position relative to the chair-like conformation of the allyl silyl ketene acetal. This result constitutes the first reported example of an exocyclic Claisen rearrangement of a cyclohexanol-derived allylic ester bearing a *Z*-substituent on the exocyclic alkene, and as such expands the utility of the rearrangement (vide supra).

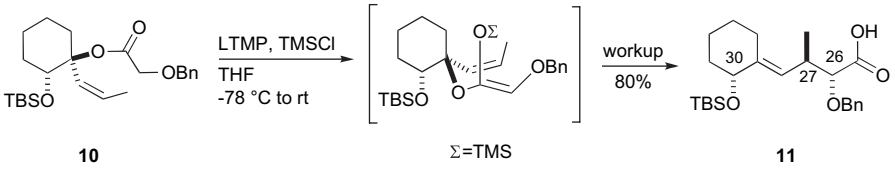
Formation of Weinreb amide **12** was followed by carbonyl addition of the vinylLi species derived from iodide **13**[5] to give enone



Scheme 3.



Scheme 4.

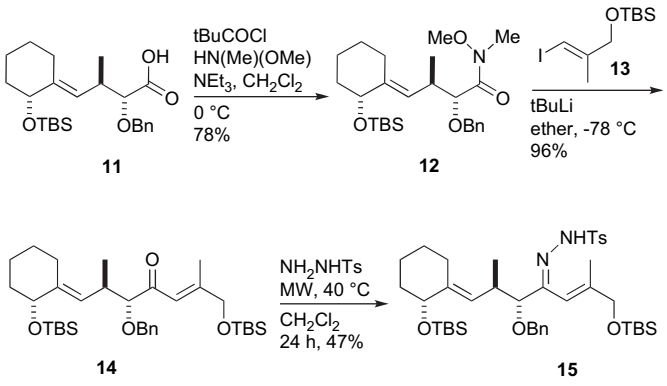


Scheme 5.

14 (Scheme 6). Treatment of the enone with tosyl hydrazide under microwave irradiation gave moderate yield of *E*-hydrazone **15**.

We next turned our attention to the application of our recently reported 1,3-reductive transposition methodology.[5] Gratifyingly, the sequence proved just as successful as in the simpler substrates that we have described previously. Diastereoselective reduction of hydrazone **15** with catecholborane in the presence of silica gel presumably afforded the C25–C26 *anti* intermediate **16**.[13] Allylic diazene rearrangement then gave diene **17** in high yield as a single diastereomer based on ^{1}H NMR analysis of the crude reaction mixture (Scheme 7). The C23–C26 *syn* configuration was assigned by analogy to earlier studies.[5] Deprotection of the bis-TBS ether afforded diol **18**.

The next step in the synthesis was directed hydrogenation of the C28–C29 alkene. Interestingly, there are only a few examples of directed hydrogenation of alkylidene type alkenes.[14–16] For diene



Scheme 6.

18, allylic strain would orient the C22–C26 side chain of the alkylidene on the same face as that of the desired hydrogenation (cf. **19**),[17] potentially hindering reaction of the alkene with the catalyst. In the event, hydrogenation using Crabtree's catalyst[18] (IrL$_n$=[Ir(cod)PCy$_3$(py)]PF$_6$) gave the desired β-C29 configuration, as well as concomitant hydrogenation of the C24–C25 alkene, to give diol **20** (Scheme 7). The C29 configuration was confirmed by the presence of the trans diaxial couplings between H-29 and H-30 and between H-29 and H$_{ax}$-34.

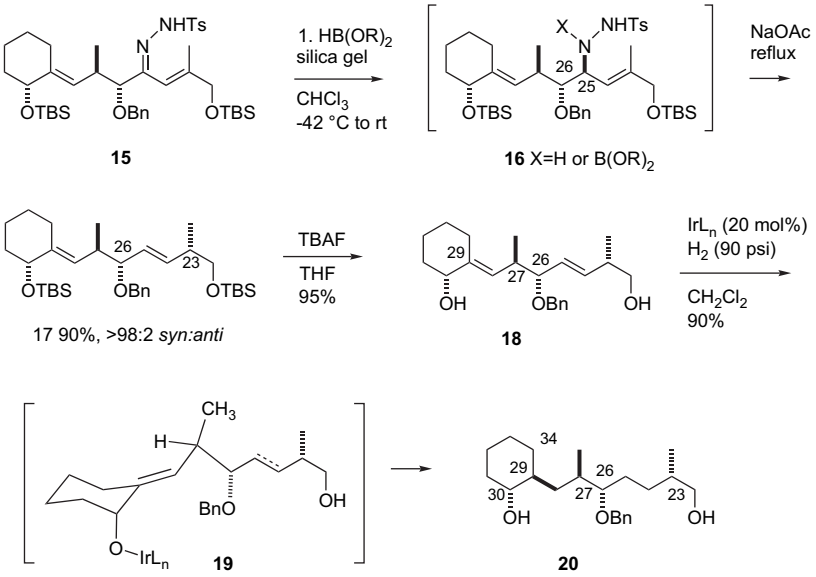
3. Conclusion

In summary, model compound **20**, containing 5 of the 7 stereocenters and all of the carbons present in the corresponding fragment of antascomicin B, has been prepared in 11 steps from commercially available 2-hydroxy-cyclohexanone using novel variants of both Ireland–Claisen and allylic diazene rearrangements. Further efforts toward the antascomicins will be published in due course.

4. Experimental section

4.1. General experimental procedures

Unless otherwise noted, all reactions were carried out under a positive pressure of nitrogen. Extractive workup is defined as extraction of the reaction mixture and the indicated aqueous solution three times with ethyl acetate or ether, washing of the combined organic extracts with saturated NaCl solution, drying of the extracts over anhydrous MgSO$_4$, and concentration in vacuo. Flash column chromatography was performed with silica gel



Scheme 7.

(40–63 μm, standard grade, Sorbent Technologies). The same silica gel was used in the indicated reaction.

4.2. Propargyl glycolate 9

TBSCl (4.9 g, 32.4 mmol) was added to a solution of *anti*-diol **8** (4.5 g, 29.5 mmol) and imidazole (2.4 g, 35.4 mmol) in DMF (10 mL) at rt. The reaction mixture was stirred for 16 h and then poured into water (5 mL). After extractive workup with hexane, the crude material was purified by flash chromatography over silica gel with 10/90 ethyl acetate/hexane to give the mono-TBS ether (6.5 g, 82%) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.22 (m, 1H), 1.3–1.8 (m, 6H), 1.83 (s, 3H), 1.95 (m, 1H), 2.65 (s, 1H), 3.4 (dd, J=10.1, 4.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.7, −4.1, 3.7, 22.8, 23.6, 25.8, 32.0, 36.8, 73.2, 77.9, 80.3, 81.2; HRMS (ESI) m/z: calcd for $C_{15}H_{28}NaO_2Si$ (MNa) 291.1859; found 291.1756.

n-Butyl lithium (4.2 mL, 2.87 M in hexane, 12.03 mmol) was added to a solution of the alcohol (2.5 g, 9.25 mmol) in dry ether (25 mL) at −78 °C. After 15 min, the acid chloride (1.7 g, 9.25 mmol) was added over 10 min to the reaction mixture. The solvent was then removed in vacuo while the mixture was allowed to warm to rt until it became a thick, albeit stirrable, slurry. After 1 h, the reaction mixture was poured into saturated $NaHCO_3$ and isolated by extractive workup. The crude material was purified by flash chromatography over silica gel with 10/90 ethyl acetate/hexane to give propargyl ester **9** (3.6 g, 95%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.93 (s, 9H), 1.32 (m, 1H), 1.51 (m, 2H), 1.66 (m, 3H), 1.88 (s, 3H), 1.89 (m, 1H), 2.39 (m, 1H), 3.96 (m, 1H), 4.08 (s, 2H), 4.67 (s, 2H), 7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.77, −4.5, 3.8, 18.1, 20.9, 21.5, 25.7, 30.8, 33.0, 67.4, 72.3, 73.1, 77.3, 80.3, 83.1, 127.9, 128.1, 128.4, 137.3, 168.2; IR (film) cm^{-1} 2253, 1758; calcd for $C_{24}H_{36}O_4Si$: C, 69.19; H, 8.71; found: C, 68.95; H, 8.81.

4.3. Allyl glycolate 10

A mixture of the propargyl ester (4.8 g, 11.6 mmol) and Pd/$BaSO_4$ (5 g, 10 wt % on $BaSO_4$, 2.3 mmol) in 50 mL of isopropyl alcohol/pyridine=4/1 was shaken in a Parr bottle under an H_2 atmosphere (90 psi) for 4 h. The reaction mixture was filtered and the filtrate concentrated in vacuo. The crude material was purified by flash chromatography over silica gel with 10/90 ethyl acetate/hexane to give allylic ester **10** (4.5 g, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.92 (s, 9H), 1.23–1.55 (m, 5H), 1.70 (m, 1H), 1.73 (d, J=6.0 Hz, 3H), 2.02 (m, 1H), 2.33 (m, 1H), 4.06 (s, 2H), 4.18 (m, 1H), 4.67 (s, 2H), 5.54 (dq, J=12.6, 6.0 Hz, 1H), 5.60 (d, J=12.6 Hz, 1H), 7.28–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.6, −5.9, 14.4, 18.0, 19.1, 21.0, 25.8, 29.4, 30.1, 66.9, 70.7, 73.2, 84.1, 125.9, 127.9, 128.0, 128.5, 131.5, 137.3, 168.0; IR (film) cm^{-1} 3029, 1756, 1658; calcd for $C_{24}H_{38}O_4Si$: C, 68.86; H, 9.15; found: C, 68.72; H, 9.23.

4.4. Pentenoic acid 11

n-BuLi (2.22 mL, 2.93 M in hexane, 6.5 mmol) was added into a solution of 2,2,6,6-tetramethylpiperidine (0.84 mL, 5.9 mmol) in THF (10 mL) at 0 °C. After 30 min, this solution was then added to a solution of TMSCl (2.25 mL, 17.7 mmol) and allylic ester **10** (1.24 g, 2.9 mmol) in THF (10 mL) over 15 min at −20 °C. The reaction mixture was then allowed to warm to rt. After 1 h, aqueous NH_4Cl was poured into the reaction mixture. After extractive workup, the crude material was purified by flash chromatography over silica gel with 50/50 ethyl acetate/hexane to give pentenoic acid **11** (1.0 g, 80%) as light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.08 (s, 3H), 0.93 (s, 9H), 1.09 (d, J=6.9 Hz, 3H), 1.3–1.6 (m, 4H), 1.7–1.9 (m, 3H), 2.46 (m, 1H), 3.0 (m, 1H), 3.89 (d, J=4.5 Hz, 1H), 4.0 (m, 1H), 4.47 (d, J=11.7 Hz, 1H), 4.78 (d, J=11.7 Hz, 1H), 5.43 (d, J=9.9 Hz, 1H), 7.3–7.4 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.7, −4.4, 18.0, 18.3, 23.4, 25.9, 26.8, 27.7, 34.8, 37.5, 72.9, 74.3, 82.2, 120.1, 127.9, 127.9, 128.4, 137.4, 142.9, 177.3; IR (film) cm^{-1} 2400–3400, 1718; calcd for $C_{24}H_{38}O_4Si$: C, 68.86; H, 9.15; found: C, 68.72; H, 9.22.

4.5. Weinreb amide 12

Trimethylacetyl chloride (1 mL, 8.15 mmol) was added to a solution of pentenoic acid **11** (3.1 g, 7.4 mmol) and NEt_3 (1.1 mL, 8.2 mmol) in CH_2Cl_2 at 0 °C. After 30 min, *N,O*-dimethylhydroxylamine hydrochloride (0.8 g, 8.2 mmol) was added, followed by NEt_3 (2.3 mL, 16.3 mmol). The reaction mixture was then allowed to warm to rt and stirred for 16 h. After extractive workup, the crude material was purified by flash chromatography over silica gel with 5/95 ethyl acetate/hexane to give the Weinreb amide **12** (2.6 g, 78%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.91 (s, 9H), 0.95 (d, J=6.0 Hz, 3H), 1.3–1.6 (m, 4H), 1.7–1.9 (m, 3H), 2.52 (m, 1H), 3.03 (m, 1H), 3.20 (s, 3H), 3.57 (s, 3H), 4.01 (m, 1H), 4.16 (m, 1H), 4.42 (d, J=12 Hz, 1H), 4.67 (d, J=12 Hz, 1H), 5.33 (d, J=9 Hz, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0, −4.8, 17.5, 18.3, 23.5, 25.9, 27.0, 27.5, 34.5, 37.5, 61.1, 71.6, 74.2, 79.5, 122.0, 127.5, 127.8, 127.9, 128.2, 138.2, 142.2; IR (film) cm^{-1} 1676; calcd for $C_{26}H_{43}NO_4Si$: C, 67.64; H, 9.39; found: C, 67.64; H, 9.44.

4.6. Enone 14

n-BuLi (1.54 mL, 2.89 M in hexane, 4.34 mmol) was added to a solution of iodide **13** (1.34 g, 4.3 mmol) in ether (5 mL) at −78 °C. After 30 min, the solution was added dropwise to Weinreb amide **12** (1.0 g, 2.17 mmol) in ether (5 mL) at −78 °C. The reaction mixture was maintained at −78 °C until no starting material remained on examining by TLC analysis. After extractive workup, the crude material was purified by flash chromatography over silica gel with 5/95 ethyl acetate/hexane to give enone **14** (1.2 g, 96%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.04 (s, 3H), 0.08 (s, 6H), 0.9 (s, 9H), 0.92 (s, 9H), 0.93 (d, J=10.2 Hz, 3H), 1.3–1.4 (m, 4H), 1.7–1.9 (m, 3H), 2.08 (s, 3H), 2.43 (m, 1H), 2.85 (m, 1H), 3.56 (d, J=6.9 Hz, 1H), 3.96 (m, 1H), 4.14 (m, 1H), 4.36 (d, J=12 Hz, 1H), 4.60 (d, J=12 Hz, 1H), 5.33 (d, J=12 Hz, 1H), 6.82 (s, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5, −5.0, −4.8, 16.2, 17.8, 18.3, 18.3, 23.6, 25.8, 25.9, 27.1, 27.4, 34.6, 37.6, 67.3, 72.2, 74.2, 89.9, 116.6, 121.4, 127.3, 127.6, 128.1, 138.2, 141.9, 158.3, 203.1; IR (film) cm^{-1} 1686, 1625, 1461; calcd for $C_{34}H_{58}O_4Si_2$: C, 69.57; H, 9.96; found: C, 69.27; H, 9.78.

4.7. *E*-Hydrazone 15

A solution of enone **14** (0.9 g, 1.5 mmol) and tosyl hydrazide (0.5 g, 3.1 mmol) was stirred under microwave irradiation (30 W) at 40 °C for 16 h. After extractive workup, the crude material was purified by flash chromatography over silica gel with 5/95 ethyl acetate/hexane to give *E*-hydrazone **15** (0.54 g, 47%) as colorless crystals, mp 113–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.09 (s, 3H), 0.10 (s, 3H), 0.65 (d, J=9 Hz, 3H), 0.88 (s, 9H), 0.91 (s, 9H), 1.2–1.5 (m, 4H), 1.60 (s, 3H), 1.6–1.8 (m, 3H), 2.34 (s, 3H), 2.59 (m, 1H), 3.63 (d, J=9 Hz, 1H), 3.93 (m, 1H), 3.97 (d, J=12 Hz, 1H), 4.08 (d, J=12 Hz, 1H), 4.13 (s, 2H), 5.19 (d, J=9 Hz, 1H), 5.85 (s, 1H), 7.07 (m, 2H), 7.2–7.4 (m, 5H), 7.72 (s, 1H), 7.84 (d, J=6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.4, −5.0, −4.8, 17.1, 17.2, 18.3, 21.5, 23.5, 25.8, 25.9, 27.1, 27.2, 29.7, 34.6, 37.5, 66.4, 70.7, 74.1, 87.0, 111.3, 122.7, 127.1, 127.4, 127.9, 128.1, 129.5, 135.3, 138.3, 141.7, 144.1, 148.2, 155.7; IR (film) cm^{-1} 3183, 1658, 1599, 1458, 1377, 1253; HRMS (ESI) m/z: calcd for $C_{41}H_{66}N_2NaO_5SSi_2$ (MNa) 777.4129, found 777.4151.

4.8. Diene 17

Catecholborane (0.2 mL, 2.1 mmol) was added dropwise to a mixture of hydrazone **15** (260 mg, 0.35 mmol) and silica gel (500 mg) in $CHCl_3$ (5 mL) at −42 °C. After 1 h, $NaOAc\cdot 3H_2O$ (856 mg, 6.3 mmol) was added and the reaction mixture heated under reflux for 16 h. The reaction mixture was poured into water and isolated by extractive workup. The crude material was purified by flash chromatography over silica gel with 5/95 ethyl acetate/hexane to give diene **15** (180 mg, 90%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 6H), 0.92 (s, 18H), 0.95 (d, J=6 Hz, 3H), 1.05 (d, J=6 Hz, 3H), 1.21–1.92 (m, 7H), 2.39 (m, 1H), 2.65 (m, 1H), 3.42 (dd, J=9, 6 Hz, 1H), 3.54 (dd, J=9, 6 Hz, 1H), 3.55 (dd, J=9, 6 Hz, 1H), 4.02 (m, 1H), 4.35 (d, J=12 Hz, 1H), 4.58 (d, J=12 Hz, 1H), 5.28 (d, J=9 Hz, 1H), 5.43 (dd, J=15, 6 Hz, 1H), 5.59 (dd, J=15, 6 Hz, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, −5.0, −4.7, 16.7, 17.3, 23.1, 25.9, 26.7, 27.6, 36.3, 37.4, 39.1, 68.1, 69.6, 74.4, 84.1, 123.3, 127.1, 127.6, 128.1, 128.3, 137.4, 139.3, 140.9; IR (film) cm^{-1} 1676, 1458; HRMS (ESI) m/z: calcd for $C_{34}H_{60}NaO_3Si_2$ (MNa) 595.4081, found 595.3969.

4.9. Diol 18

A solution of bis-TBS ether **17** (0.1 g, 0.18 mmol) and NBu_4F (0.53 mL, 1 M in THF, 0.51 mmol) was stirred for 2 h. After extractive workup, the crude material was purified by flash chromatography over silica gel with 50/50 ethyl acetate/hexane to give diol **18** (57 mg, 95%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, J=6 Hz, 3H), 1.01 (d, J=9 Hz, 3H), 1.3–1.5 (m, 3H), 1.7–1.9 (m, 4H), 2.35 (m, 2H), 2.68 (m, 1H), 3.36 (dd, J=12, 9 Hz, 1H), 3.54 (m, 2H), 3.73 (m, 1H), 4.0 (m, 1H), 4.35 (d, J=12 Hz, 1H), 4.58 (d, J=12 Hz, 1H), 5.17 (d, J=9 Hz, 1H), 5.42 (m, 2H), 7.2–7.4 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 16.6, 23.1, 26.7, 27.3, 35.8, 36.4, 39.7, 67.3, 70.0, 73.5, 83.6, 123.7, 127.4, 127.6, 128.2, 129.6, 137.2, 138.9, 141.2; IR (film) cm^{-1} 3353, 3029, 1665, 1450; HRMS (ESI) m/z: calcd for $C_{22}H_{36}NaO_3$ (MNa) 371.2664, found 371.2573.

4.10. Antascomicin B model 20

A mixture of diol **18** (57 mg, 0.17 mmol) and Crabtree's catalyst (13 mg, 0.03 mmol) in CH_2Cl_2 (5 mL) was shaken in a Parr bottle under an H_2 atmosphere (90 psi) for 1 h. After extractive workup, the crude material was purified by flash chromatography over silica gel with 50/50 ethyl acetate/hexane to give model compound **20** (50 mg, 87%) as colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (d, J=5.4 Hz, 6H), 1.2–2.08 (m, 17H), 3.13 (dt, J=5.4, 10.8 Hz, 1H), 3.24 (q, J=5 Hz, 1H), 3.44 (d, J=5.9 Hz, 2H), 4.45 (d, J=11.7 Hz, 1H), 4.53 (d, J=11.7 Hz, 1H), 7.32 (m, 5H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 16.4, 16.8, 24.9, 25.7, 26.2, 29.0, 31.8, 33.0, 35.6, 35.8, 37.6, 43.6, 68.1, 71.4, 76.2, 82.6, 127.6, 128.0, 128.4, 139.0; IR (film) cm^{-1} 3359, 1451, 1051; HRMS (ESI) m/z: calcd for $C_{22}H_{36}NaO_3$ (MNa) 371.2562, found 371.2573.

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Supplementary data

^{1}H and ^{13}C NMR spectra of compounds **9**–**12**, **14**, **15**, **17**, **18**, and **20**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.05.070.

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