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Convergent assembly of aldol linkages. A study of the stereoselective nitrile oxide cycloaddition reaction

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Abstract

The aldol equivalency of a stereoselective nitrile oxide cycloaddition is exploited in the development of a general synthetic strategy to the polyene macrolide antibiotics. © 2000 Elsevier Science Ltd. All rights reserved.

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Within the polyene macrolide antibiotics, the heptaene/pseudoheptaene subfamily has gained prominence as a consequence of their clinically important antifungal activity.[1] We have recently reported on our successful efforts to develop a synthetic strategy that may be generally applicable to this structural sub-group.[2] As illustrated (Fig. 1), significant structural homology exists among these compounds, with most of the variation residing in the C1–C10 segment of the macrocycle. These structural relationships guided the design of our synthetic approach to amphotericin B. In order to realize generality in our strategy, a convergent approach was adopted that featured fusion of the conserved and variable segments of the macrocycle. As a result of these considerations, polyol segment **1** was identified as a key intermediate that would allow the fusion of the conserved and variable carbon segments.

Successful execution of our strategy hinged on an effective means of forming the C13–C15 aldol linkage. As the shaded region of segment **1** highlights, standard aldol construction of the C15 alcohol is not viable as this would require a condensation reaction with an enolizable β-dicarbonyl component. In a search for alternative approaches, we were attracted to the aldol equivalency of the isoxazoline adducts **2** resulting from nitrile oxide cycloadditions.[3] Application of this method to the assembly of polyol segment **1** requires that this cycloaddition reaction proceed in both an *efficient* and *stereoselective* manner to afford the desired C15 stereocenter without undue loss of valuable synthetic precurors. With these concerns in mind, we embarked upon model studies to optimize these reaction parameters.

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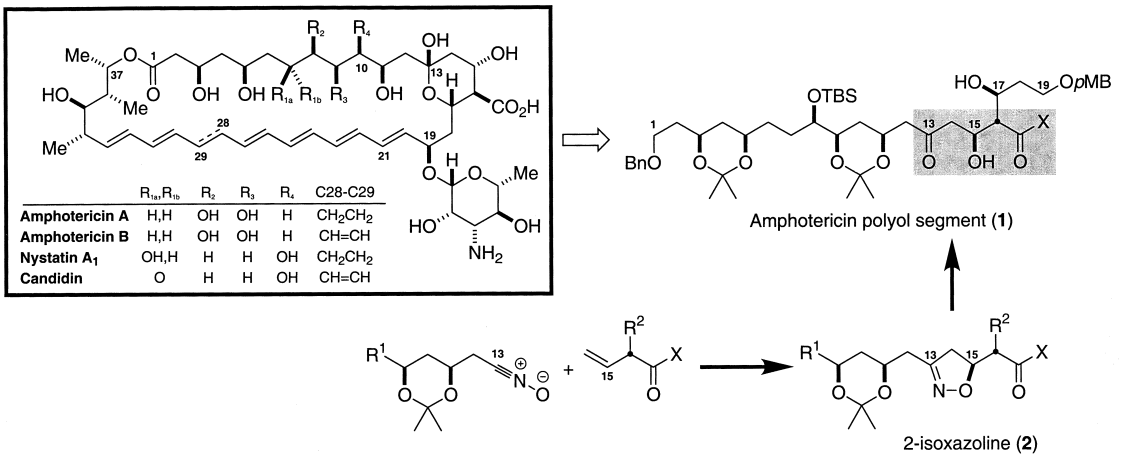
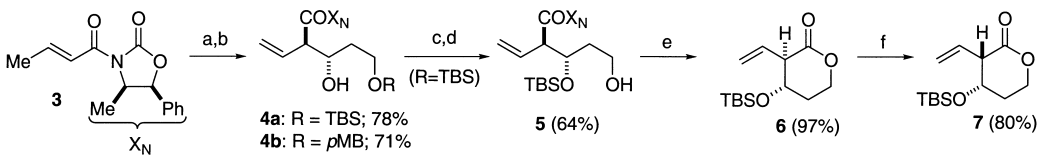


Figure 1.

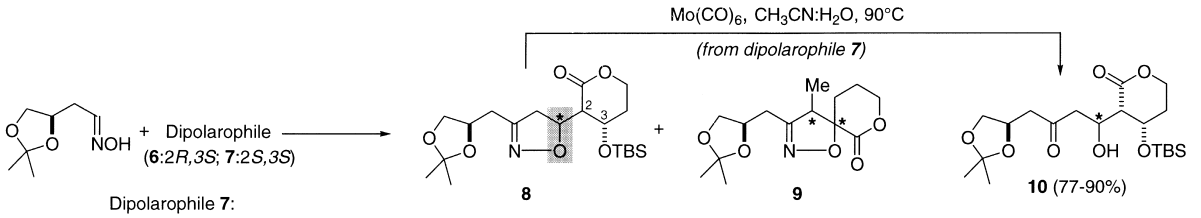
A survey of reported stereoselective nitrile oxide cycloaddition reactions clearly indicates that the dipolarophile component dominants steric course of the reaction.[4] Armed with this observation, we embarked upon studies to identify an asymmetric dipolarophile that would be generally applicable to the assembly of the (psuedo)heptaene macrocrolactones. A C14–C19 dipolarophile was efficiently prepared in the manner shown in Scheme 1. An Evans' aldol condensation[5] establishes the desired C16 and C17 stereochemistry (**3**→**4a**/**b**) in an adduct (**5**) which, following selective protecting group manipulation, affords lactone **6**. It was interesting to observe the sensitivity of this product to base-induced epimerization. In fact, while attempting to obtain a deprotected dipolarophile for study, complete isomerization to **7** resulted, presumably as a consequence of a preferred boat-like conformation of the lactone ring.



Scheme 1. (a) $^{n}Bu_2BOTf$, Et_3N, CH_2Cl_2; (b) $ROCH_2CH_2CHO$, 95% ds, R = TBS, 78%, R = *p*MB, 71%; (c) TBSOTf, Et_3N, CH_2Cl_2, 0°C; (d) HF·pyridine, pyridine, rt, 64% (two steps); (e) ^{t}BuMgBr, THF, –78→–25°C; (f) HF·pyridine, pyridine, rt

While not appropriate for the synthesis of amphotericin B, cycloaddition studies using lactone **7** were instructive. We chose aldoximes derived from D- or L-malic acid as model dipole precursors,[6] anticipating that asymmetry in this component would exert a small influence on cycloaddition stereoselection. Several sets of standard conditions for the generation of nitrile oxides were applied to the *R*-oxime to give the results shown (Scheme 2). When basic dehydrohalogenation conditions were employed, the desired product **8** was isolated in poor yields with the major product being a spirocyclic adduct **9**, resulting from double bond isomerization in the dipolarophile. Fortunately, the use of $(^{n}Bu_3Sn)_2O$ to promote dehydrohalogenation[7] led to clean cycloaddition with no isomerized adduct. While acceptably efficient, this cycloaddition showed unacceptable stereoselectivity. It was also disappointing to find that use of the dipolarophile

having the proper stereochemistry (**6**) gave similarly modest levels of stereoselectivity. Nevertheless, the aldol equivalency of these cycloaddition reactions was demonstrated by the efficient $Mo(CO)_6$-promoted cleavage/hydrolysis[8] of the isoxazoline adduct to the corresponding β-hydroxy ketone **10**.

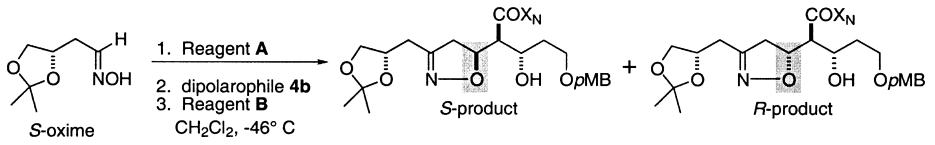


Dipolarophile **7**:			
NaOCl, CH_2Cl_2	<15%	(3:1)	30%
NCS; Et_3N, pyr. (cat.), $CHCl_3$	23%	(4.5:1)	55%
NCS; $(^nBu_3Sn)_2O$, CH_2Cl_2	**64%**	**(1.5:1)**	**0%**
Dipolarophile **6**:			
NCS; $(^nBu_3Sn)_2O$, CH_2Cl_2	**74%**	**(1.12:1)**	**0%**

Scheme 2.

An investigation of other dipolarophiles was initiated in an effort to improve the diastereoselection of this cycloaddition process. Fortunately, it was found that the Evans' aldol product **4b** could be used, *even without protection of the putative C17 alcohol*. The advantages of this dipolarophile were immediately apparent. First, the double bond in this substrate was far less prone to isomerization, thus allowing the use of Et_3N as a base for nitrile oxide formation. More importantly, stereoselectivity was significantly improved (see Table 1). The use of halosuccinimides with Et_3N or $(^nBu_3Sn)_2O$ to effect dehydrohalogenation gave similar levels of diastereoselection but with modest yields reflecting difficulties in removing succinimide from the product (entries 1–4). It bears noting that the yield of this cycloaddition is strongly effected by the order of addition of the dipolarophile with the halosuccinimide (entries 3 and 4). Use of ^{t}BuOCl as the chlorinating

Table 1

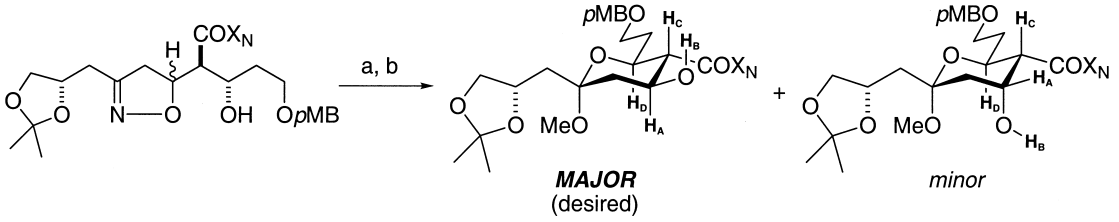


Entry	Reagent A (equiv.)	Equiv. 4b	Reagent B (equiv.)	d.s.[a]	Yield[b]
1[c]	NCS (1.5)	1.5	Et_3N (0.5)	68:32	43%
2	NBS (1.1)	2.5	Et_3N (2.5)	75:25	60%
3	NBS (1.1)	1.5	$(^nBu_3Sn)_2O$ (0.52)	63:37	41%
4[d]	NBS (1.1)	1.5	$(^nBu_3Sn)_2O$ (0.52)	62:38	18%
5	^{t}BuOCl (1.2)	1.5	$(^nBu_3Sn)_2O$ (0.8)	88:12	46%
6	**^{t}BuOCl (1.05)**	**1.5**	**$(^nBu_3Sn)_2O$ (0.5)**	**88:12**	**73%**
7	**$(^nBu_3Sn)_2O$ (0.55)**	**1.5**	**^{t}BuOCl (1.0)**	**88:12**	**71%**

[a]determined by ^{1}H NMR analysis. [b]following chromatographic (SiO_2) purification. [c]reaction run at 0° C. [d]inverse addition of NBS.

agent led to significant improvements in both yield and stereoselectivity (entry 5). It was ultimately found that good yields and diastereoselectivity could be obtained using approximately stoichiometric amounts of the reagents and a modest excess of the dipolarophile (entries 6 and 7).

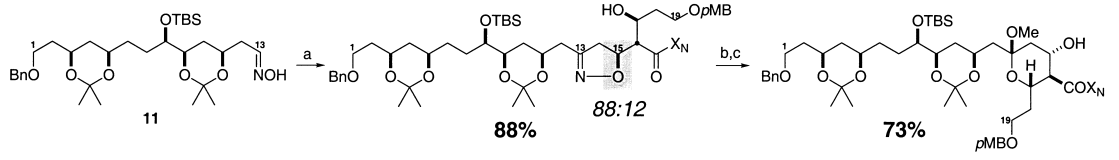
With an effective protocol identified for the cycloaddition, it remained to establish the stereochemistry of the cycloadduct. This was accomplished as depicted in Scheme 3. The isomeric β-hydroxy ketones could be unmasked then trapped as their cyclic mixed acetal through the agency of $(MeO)_3CH$. The resultant conformationally biased diastereomers were examined by various NMR methods to establish stereochemistry.[9] With the acetal methoxy group occupying the steric/stereoelectronically favored axial position, two distinct substitution patterns could be identified. Notably, the major isomer exhibited a clear NOE effect between H_A–H_D and H_B–H_C, as well as J-coupling values consistent with equatorial substitution about the ring. As a result, the major diastereomer of the nitrile oxide cycloaddition could be assigned to the desired S-stereo-



Scheme 3. (a) $Mo(CO)_6$, 10% H_2O/MeCN, 80°C; (b) PPTs, MeOH:$(MeO)_3CH$ (1:1), rt

chemistry.

With these encouraging results in hand, the optimized cycloaddition conditions were applied to the synthetic C1–C13 fragment of amphotericin B[2] (**11**, Scheme 4). In the event, cycloaddition using 3 equivalents of dipolarophile **4b**[10] proceeded in an excellent 88% yield with diastereoselectivity identical to the model studies. This latter result lends credence to our anticipation that the dipolarophile would govern the stereochemical course of this bond-forming reaction. Cleavage/hydrolysis of the isoxazoline adduct followed by cyclization/acetalization[11] proceeded smoothly to afford the intact C1–C19 fragment of amphotericin B. As we previously reported, this material



Scheme 4. (a) *Sequential addition*: (i) $(^nBu_3Sn)_2O$; (ii) olefin **4b** (3 equiv.); (iii) ^{t}BuOCl; (b) $Mo(CO)_6$, 10% H_2O/MeCN, 70°C; (c) $MeC(OMe)_3$, PPTs, MeOH, rt

could be incorporated into the polyene macrocycle to complete the total synthesis.[2,12]

This study has demonstrated a remarkably effective means of linking highly functionalized carbon frameworks as part of a strategy for the synthesis of complex natural products. In the present case, the nitrile oxide cycloaddition contributes to a general strategy to the polyene macrolide antibiotics. Given the stereodirecting influences of the dipolarophile **4b**, it can be anticipated that other dipole precursors may be used to allow synthetic access to other members of this class of compounds (see Fig. 1).

Acknowledgements

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9. Both diastereomers were analyzed using 1D ^{1}H, COSY, and NOESY experiments to obtain vicinal J-coupling values, proton connectivity, and spatial relationships, respectively.
10. An examination of molar dipolarophile:dipole ratios from 1:1 to > 5:1 revealed that the yield was optimized at 3:1.
11. Mixed acetal formation was significantly improved when $CH_3C(OMe)_3$ was used in place of $HC(OMe)_3$.
12. Physical data for selected new compounds. Compound **4a**: $[\alpha]_D = +20.82$ (*c* 3.08, CCl_4); IR (film) 3400, 2940, 2920, 1775, 1680, 1450, 1340, 1250, 1190, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.02 (s, 4H), 0.82 (d, 3H, J = 6.3 Hz), 0.85 (s, 9H), 1.88 (m, 2H), 3.81 (m, 3H), 4.21 (m, 1H), 4.50 (dd, 1H, J = 4.2, 8.7 Hz), 4.76 (m, 1H), 5.27 (m, 2H), 5.64 (d, 1H, J = 7.2 Hz), 6.01 (m, 1H), 7.23–7.36 (m, 5H); ^{13}C ($CDCl_3$, 75 MHz) δ –5.03, 14.67, 18.65, 26.34, 35.60, 36.58, 53.40, 55.33, 59.66, 62.09, 71.74, 79.30, 100.25, 120.81, 126.06, 129.14, 129.23, 132.26, 133.60, 153.06, 173.57. Compound **6**: $[\alpha]_D = +33.87°$ (*c* 1.42, CCl_4); IR (film) 2975, 2960, 2822, 1722, 1508, 1299, 1252, 1212, 1160, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.06 (s, 6H), 0.88 (s, 9H), 1.77 (m, 1H), 2.14 (m, 1H), 3.20 (dd, 1H, J = 5.8, 7.2 Hz), 4.03 (dd, 1H, J = 4.8, 8.4 Hz), 4.29 (ddd, 1H, J = 4.5, 8.7, 12.4 Hz), 4.55 (dt, 1H, J = 3.9, 10.8 Hz), 5.26 (m, 2H), 5.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –4.40, –4.25, 18.32, 26.06, 29.96, 55.02, 65.47, 68.92, 120.11, 133.84, 171.43; anal. calcd for $C_{13}H_{24}O_3Si$: C, 61.13, H, 9.08; found: 61.32; H, 9.25. Compound **7**: $[\alpha]_D = –60.82$ (*c* 1.00, $CHCl_3$); mp = 44–46° C; IR (CCl_4) 3005, 2980, 2960, 1720, 1505, 1465, 1410, 1200, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.05 (s, 6H), 0.80 (s, 9H), 1.90 (m, 1H), 2.12 (m, 1H), 3.10 (dd, 1H, J = 3.3, 8.1 Hz), 4.31 (m, 2H), 4.60 (dt, 1H, J = 10.2, 11.1 Hz), 5.24 (dd, 2H, J = 10.2, 17.4 Hz), 6.02 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –4.75, –4.25, 18.42, 26.09, 31.63, 53.04, 65.78, 69.75, 119.60, 133.90, 171.85; anal. calcd for $C_{13}H_{24}O_3Si$: C, 61.13, H, 9.08; found: C, 61.00, H, 9.13. S-product (Table 1): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (d, 3H, J = 6.6 Hz), 1.32 (s, 3H), 1.41 (s, 3H), 1.78 (m, 2H), 2.01 (s, 1H), 2.57 (m, 2H), 3.09 (m, 2H), 3.64 (m, 6H), 3.75 (s, 3H), 4.10 (m, 1H), 4.27 (m, 1H), 4.33 (M, 1H), 4.72 (S, 2H), 4.65 (dd, 1H, J = 6.6, 9.6 Hz), 4.75 (m, 1H), 4.92 (dd, 1H, J = 7.2 Hz), 6.85 (d, 2H, J = 8.4 Hz), 7.22–7.42 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.45, 14.59, 25.78, 25.93, 27.31, 27.39, 32.71, 34.49, 44.22, 53.31, 55.53, 68.67, 71.34, 73.49, 73.67,79.16, 80.69, 100.65, 114.30, 126.01, 126.28, 129.00, 129.23, 129.51, 129.56, 129.74, 129.95, 130.25, 133.64, 153.29, 157.06, 172.43; HRMS (M+1): anal. calcd for $C_{32}H_{40}N_2O_8$: 596.2734; found: 596.2781. Major mixed acetal (Scheme 3): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (d, 3H, J = 6.6 Hz), 1.35–1.45 (s, 6H), 1.6–2.1 (m, 5H), 2.19 (dd, 1H, J = 4.59, 12.65 Hz), 2.52 (d, 1H, J = 10.2 Hz), 3.14 (s, 3H), 3.5–3.8 (m, 7H), 3.9–4.3 (m, 4H), 4.40 (d, 2H, J = 3.9 Hz), 4.65 (m, 1H), 5.17 (d, 1H, J = 7.2 Hz), 6.84 (d, 2H, J = 9.0 Hz), 7.21 and 7.40 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.72, 26.20, 27.28, 30.10, 30.12, 33.56, 40.13, 43.27, 48.01, 52.89, 55.57, 55.89, 66.47, 68.74, 69.66, 70.86, 72.65, 73.33, 100.10, 108.92, 114.17, 126.06, 129.11, 129.22, 129.97, 130.74, 133.32, 154.69, 159.67, 173.48; anal. calcd for $C_{33}H_{43}NO_{10}$: 613.2785; found: 613.284.