ORGANIC LETTERS

2004
Vol. 6, No. 14
2485−2488

Stereochemically Rich Pentaketides from Bis(isoxazolines): A General Strategy for Efficient Polyketide Synthesis

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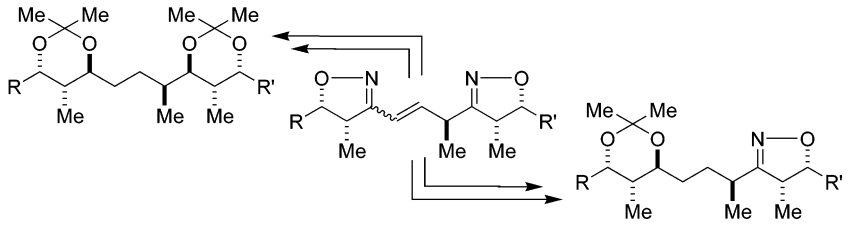
Received May 21, 2004

ABSTRACT



A strategy based on diastereoselective dipolar cycloaddition reaction of nitrile oxides and allylic alcoholates has been applied to the synthesis of bis(isoxazolines) that are precursors to polyketide fragments. These intermediates can be elaborated into protected polyols by chemoselective reductive opening of each isoxazoline sequentially or, alternatively, both simultaneously, potentially providing access to all stereoisomers of this carbon skeleton.

The total synthesis of polyketide natural products remains a challenging area of modern organic chemistry that is driven by the need to produce these compounds in sufficient quantities for biological evaluation, chemical biology applications, and development of new medicines. Furthermore, the structural diversity encompassed by this class of natural products has provided a fertile arena for the development of new synthetic methodology. For example, the last 20 years has seen an explosion of applications of the now traditional aldol and allylation/crotylation chemistry.[1−3]

We have been interested in the development of new strategies that would provide a general and complementary approach to polyketide construction. In this context, we recently reported the application and development of the nitrile oxide cycloaddition of magnesiated allylic alcohols to furnish dipropionate fragments.[4,5] In this approach, which was pioneered by Curran throughout the 1980s,[6] the Δ^2-isoxazoline serves as a masked β-hydroxy ketone that is

(1) For recent reviews on the aldol reaction, see: (a) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Eur. J.* **2002**, *8*, 36−44. (b) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vol. III, pp 997−1065. (c) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergman: Oxford, 1991; Vol. 2, pp 133−179. (d) Heathcock, C. H. In *Comprehensive Organic Synthesis, Vol. 2*; Trost, B. M., Fleming, I., Eds.; Pergman: Oxford; 1991; pp 181−238. (e) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergman: Oxford; 1991; Vol. 2, pp 239−275. (f) Cowden, C. J.; Paterson, I. In *Organic Reactions*; Paquette L. A.; Wiley & Sons: New York, 1997; Vol. 51, pp 1−200.

(2) For reviews on allylation/crotylation see: (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; pp 299−401; (b) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; pp 403−490.

(3) Other recent nonaldol approaches: (a) Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365−377. (b) Sneddon, H. F.; Gaunt, M. J.; Ley, S. V. *Org. Lett.* **2003**, *5*, 1147−1150. (c) Hanessian, S.; Ma, J.; Wang, W. *Tetrahedron Lett.* **1999**, *40*, 4627−4630. (d) Jung, M. E.; van den Heuvel, A. *Org. Lett.* **2003**, *5*, 4705−4705.

(4) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082−2085.

(5) For a lead reference on Kanemasa's work on the Mg^{2+}-mediated nitrile oxide cycloaddition, see: Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324−2339.

10.1021/ol0490633 CCC: $27.50
Published on Web 06/18/2004

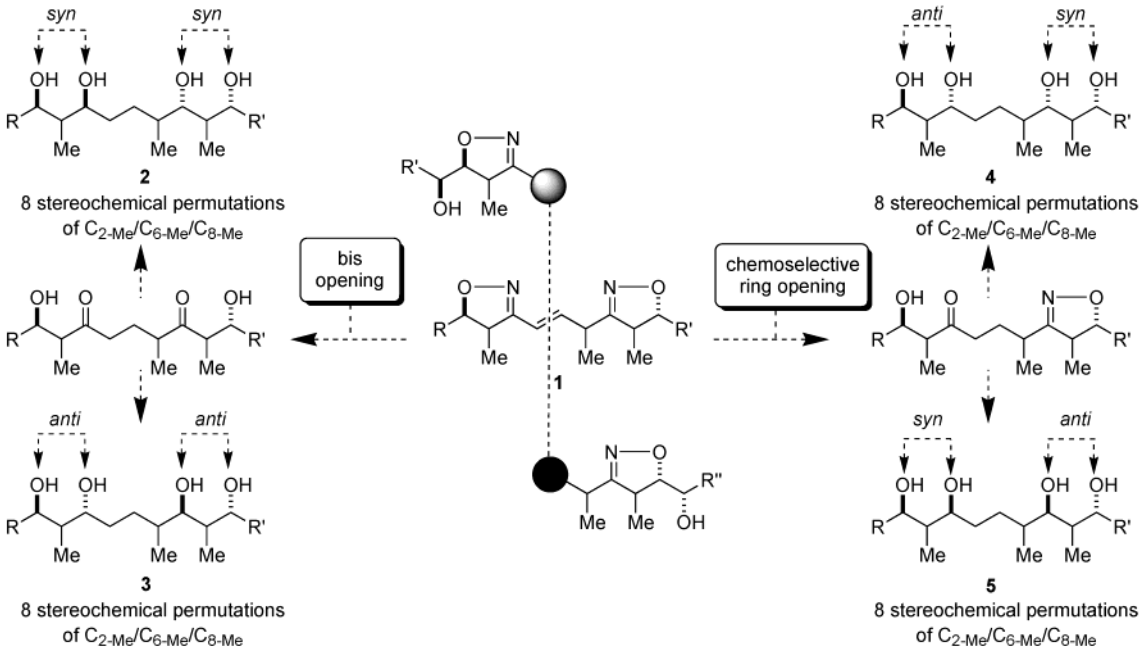


Figure 1. Bis(isoxazoline) approach to polyketide construction.

revealed by reduction of the N−O bond followed by imine hydrolysis. Advantages of this strategy include facile, diastereoselective access to *anti*- and *syn*-aldol as well as methyl ketone aldol equivalents using a single reaction protocol. Our earlier account concluded by suggesting that use of bis(isoxazolines) may prove to be a viable approach to the preparation of longer polyketide fragments. However, the key issue of manipulating such systems (through bis-reductive opening of a bis(isoxazoline)) was not addressed. In this communication, we document our investigations into the preparation and elaboration of fragments incorporating bis(isoxazolines), and, importantly, we document the ability to carry out their chemoselective, stepwise opening which considerably expands access to polyketides subunits found in natural products.

Our retrosynthetic analysis of several polyketide natural products suggested that a diverse group of polyol building blocks could be derived from a common class of linear fragments incorporating bis(isoxazoline) intermediates, irrespective of the relative stereochemical pattern (Figure 1). For example, bis(isoxazoline) **1** would permit access to compounds **2** or **3**, which contain syn,syn or anti,anti stereotetrads, respectively, by simultaneous unmasking and manipulation of both latent β-hydroxy ketones. Such a strategy can only be employed if the relative stereochemical relationships between pairs of 1,3-alcohols are identical, i.e., both syn or both anti. This constraint could be removed provided that chemoselective unmasking and manipulation of each β-hydroxy ketone could be attained. This would furnish fragments **4** and **5**, which possess anti,syn or syn,anti stereotetrads. In such a scenario, the pairwise stereochemical relationships of 1,3-diol subunits need not be identical. The most versatile implementation of this strategy would involve coupling of the various stereochemical permutations of monoisoxazoline fragments through a reaction that would not be ostensibly dependent on the stereochemical pattern of the individual subunits. Thus, we needed to address two key compelling issues: (1) facile coupling of isoxazoline modules to afford bis(isoxazolines) and (2) successful chemoselective manipulation of each isoxazoline ring.

To initiate our investigation of this approach to polyketide construction, we prepared appropriately substituted isoxazoline building block partners that could be conveniently coupled via an olefination reaction. Using our previously described adaptation of Kanemasa's nitrile oxide cycloaddition, isoxazoline **8** was prepared from readily available oxime **6** and allylic alcohol **5** as a single diastereomer in 60% yield over four steps (Scheme 1). Similarly, sulfone **11** was prepared from chiral allylic alcohol **10** and oxime **9** as a single diasteromer in 72% yield over five steps. Condensation of aldehyde **8** and sulfone **11** via a Kocienski-modified Julia−Lythgoe olefination[7] provided bis(isoxazolines) **12a** and **12b** in 96% yield with an inconsequential *E*/*Z* ratio of 30:70.[8]

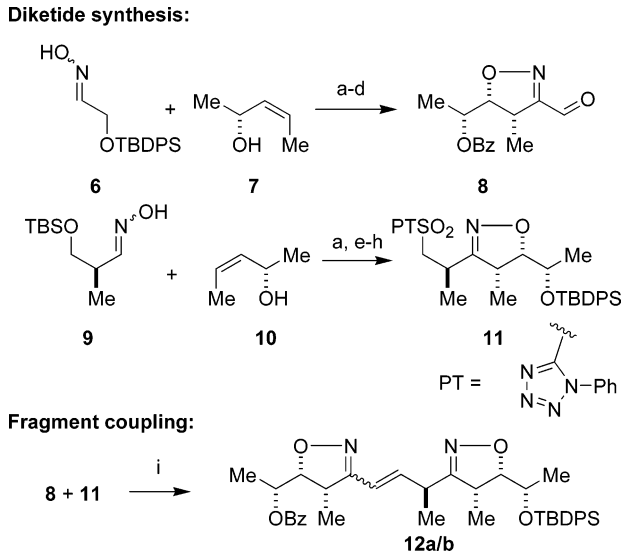
Elaboration of bis(isoxazoline) **12a/b** into protected polyketide fragments was subsequently examined. Thus, hydrogenation of the mixture of olefin isomers proceeded in 97% yield (Scheme 2) to give saturated bis(isoxazoline)

(6) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024−4026.

(7) (a) Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, *3*, 365−366. (b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563−2585.

(8) The lack of trans selectivity in this reaction was unexpected. For a range of reaction conditions employed in an effort to improve the selectivity of this coupling reaction, see Supporting Information.

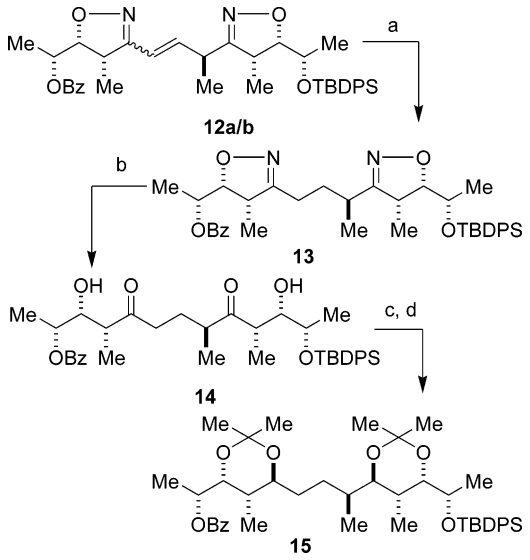
Scheme 1. Synthesis of Bis(isoxazoline) **12**[a]



[a] Conditions: (a) (i) *t*BuOCl, **6** or **9**, CH_2Cl_2; (ii) **7** or **10**, EtMgBr, *i*PrOH, CH_2Cl_2, 0 °C. (b) BzCl, Et_3N, DMAP, CH_2Cl_2, 93%. (c) TBAF, THF, 93%. (d) Dess−Martin periodinane,[9] CH_2Cl_2, 88%. (e) TBDPSCl, im, DMF, 98%. (f) AcOH, THF, H_2O, 95%. (g) PTSH, Ph_3P, DEAD, THF, 99%. (h) $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, H_2O_2, EtOH, 92%. (i) **11**, KHMDS, THF, −78 °C, then **8**, 96%.

13. Both isoxazolines could then be converted to the corresponding β-hydroxy ketones in 85% yield by subjection to Curran's conditions (H_2, Ra/Ni, $B(OH)_3$).[10] Directed reduction of both hydroxy ketones using the procedure of Evans[11] and protection of the derived tetraol provided bis-(acetonide) **15** in 70% overall yield for the sequence commencing with **12a/b**.

Scheme 2. Synthesis of Bis(acetonide) **15**[a]

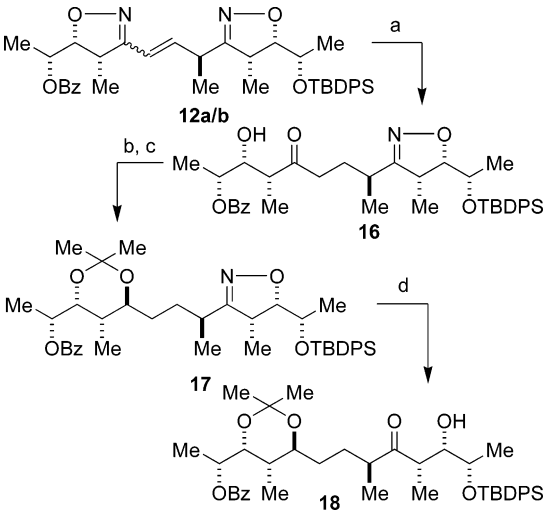


[a] Conditions: (a) H_2, Pd−C, EtOH, 97%; (b) H_2, Raney-Ni, MeOH/H_2O, $B(OH)_3$, 85%; (c) $Me_4NBH(OAc)_3$, AcOH, MeCN; (d) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH; 85%, two steps.

The sequence leading from **12a/b** to **15** represents a rapid, highly convergent alternative route to complex polyketide building blocks that is not based on aldol chemistry. However, as outlined above, a key limitation of the approach outlined in Scheme 2 is that the pairwise stereochemical relationships between the 1,3-diols are not independent (i.e., for **15** both are anti). A significant improvement of this strategy would be the ability to unmask each latent β-hydroxy ketone in sequence and modify it appropriately. We have previously noted that 3-alkenyl isoxazolines can be converted to the corresponding β'-hydroxy α,β-unsaturated ketone by treatment with excess SmI_2 and $B(OH)_3$ in THF.[12] Moreover, this system was shown to reduce saturated isoxazolines at a slower rate. Our interest in selectively manipulating the isoxazolines in **12a/b** presents an opportunity to examine whether the process would be chemoselective for a structure incorporating two different isoxazolines, a prospect that had remained untested in our original study.

We were delighted to observe (Scheme 3) that a modification of our previous procedure afforded the conversion of **12a** and **12b** to the desired isoxazoline **16** in 55−70% yield, with starting material **12a/b** accounting for the remainder of the mass balance (25−40%).[13] With the stage set for modification of each β-hydroxy ketone separately, directed

Scheme 3. Synthesis of Ketone **18**[a]



[a] Conditions: (a) SmI_2, THF/H_2O, 55−70%; (b) $Me_4NBH(OAc)_3$, AcOH, MeCN; (c) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH; 85%, two steps; (d) H_2, Raney-Ni, MeOH/H_2O, $B(OH)_3$, 90%.

(9) Dess, P. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
(10) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826−5833.
(11) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939−5942. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.
(12) Bode, J. W.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 1587−1590.
(13) In previous studies, we have shown that the presence of water in the reaction mixture employed for the reductive opening of unsaturated isoxazolines, analogous to **12a/b**, leads to concomitant reduction of the olefin; see 12. For a comparison of relative rates of reduction of α,β-unsaturated esters, ketones, and imines by a related Sm(II) reductant, see: Dahlen, A.; Hilmersson, G. *Chem. Eur. J.* **2003**, *9*, 1123−1128.

reduction of the ketone followed by a protection step provided acetonide **17** in 85% yield as a single diastereomer. Finally, isoxazoline **17** was transformed to ketone **18** in 90% yield. This ketone can be left as is or can then, in principle, be reduced to either the corresponding 1,3-*syn*- or 1,3-*anti*-diols at will.

As an additional demonstration of this strategy, we have specifically applied this chemistry to the synthesis of **23**, which serves as a model system incorporating the stereochemical pattern found in C22−C33 polyol subunit of aplyronine A[14] (Figure 2). Thus, isoxazoline building blocks

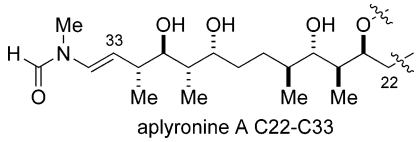
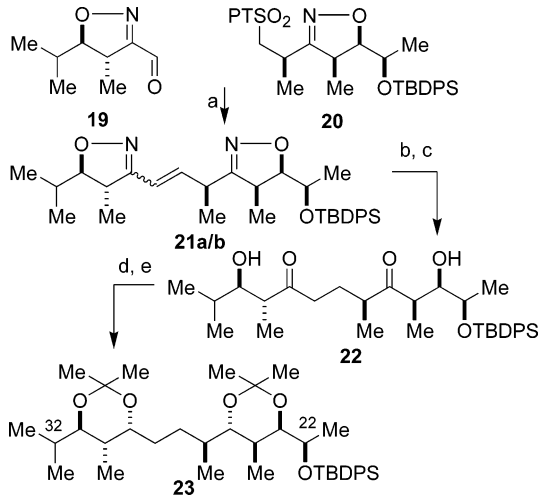


Figure 2. C22−C23 fragment of aplyronine A.

19 and **20** were prepared using the nitrile oxide cycloaddition methodology and coupled in 75% yield to provide a 45:55 mixture of olefins **21a** and **21b** (Scheme 4). Subsequent olefin reduction, isoxazoline ring opening, directed reduction of the resulting ketones, and protection of the tetraol gave bis(acetonide) **23** in 50% yield over four steps.

In summary, we have shown that pentaketide fragments are efficiently accessed from bis(isoxazoline) intermediates prepared from aldehyde and sulfone isoxazoline coupling partners. Since each stereocenter of fragments **15** or **18** is set by the choice of chiral allylic alcohol and oxime employed in the dipolar cycloaddition reaction, all 128 stereoisomers of this carbon skeleton could be accessed using a single battery of chemical transformations. This is made possible by the ability to manipulate an unsaturated isoxazoline subunit within a larger fragment that contains a saturated isoxazoline. Furthermore, the ability of unmasking each β-hydroxy ketone separately not only facilitates installation of pendant side chains present within many polyketides (e.g., esters, amino acids) but it also provides access to other polyketide fragments represented by the sphinxolide,[15] my-

Scheme 4. Synthesis of Aplyronine C22−C33 Polyol[a]



[a] Conditions: (a) KHMDS, THF, 75%, E/Z = 45:55; (b) H_2, Pd−C, EtOH, 96%; (c) H_2, Raney-Ni, MeOH/H_2O, $B(OH)_3$, 72%; (d) $Me_4NBH(OAc)_3$, AcOH, MeCN; (e) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH; 71%, two steps.

calolide,[16] ulapualide,[17] halichondramide,[18] and potentially bafilomycin,[19] concanamycin,[20] and formamicin[21] skeletons. Efforts to apply this strategy to such endeavors are currently underway.

Acknowledgment. We thank the Swiss National Science Foundation for generous support of this research. L.D.F. thanks Natural Sciences and Engineering Research Council of Canada for a postdoctoral fellowship.

Supporting Information Available: Detailed descriptions of experimental procedures and analytical data for compounds **6**, **8**, and **11**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Yamada, K.; Ojika, M.; Ishigaki, T.; Yoshida, Y.; Ekimoto, H.; Arakawa, M. *J. Am. Chem. Soc.* **1993**, *115*, 11020−11021

(15) Guella, G.; Mancini, I.; Chiasera, G,; Pietra, F. *Helv. Chim. Acta* **1989**, *72*, 237−246.

(16) Fusetani, N.; Yasumuro, K.; Matsunaga, S.; Hashimoto, K. *Tetrahedron Lett.* **1989**, *30*, 2809−2812.

(17) Roesener, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 846−847.

(18) Kernan, M. R.; Faulkner, D. J. *Tetrahedron Lett.* **1987**, *28*, 2809−2812.

(19) Werner, G.; Hagenmaier, H.; Drautz, H.; Baumgartner, A.; Zaehner, H. *J. Antibiot.* **1984**, *37*, 110−117.

(20) Westley, J. W.; Liu, C. M.; Sello, L. H.; Evans, R. H.; Troupe, N.; Blount, J. F.; Chiu, A. M.; Todaro, L. J.; Miller, P. A. *J. Antibiot.* **1984**, *37*, 1738−1740.

(21) Igarashi, M.; Nakamura, H.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 932−936.