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Versatile Configuration-Encoded Strategy for Rapid Synthesis of 1,5-Polyol Stereoisomers

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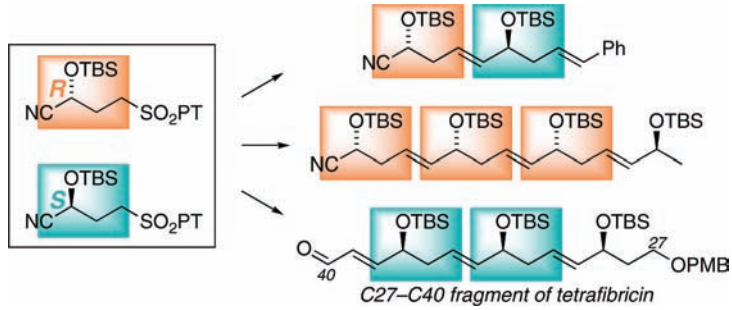
ABSTRACT



The isolated stereogenic centers of 1,5-polyol-containing natural products present challenges to synthesis and structure determination. To address this problem, a configuration-encoded strategy defines each configuration within a simple 4-(arylsulfonyl)butyronitrile building block, a repeat unit that is reliably and efficiently coupled in iterative fashion to afford 1,5-polyols of defined stereochemistry. For example, the C27−C40 subunit of tetrafibricin is prepared in five steps and 42% yield. This strategy is amenable to rapid and unambiguous preparation of all configurational permutations of 1,5-polyols with equal facility.

Chiral 1,5-polyol substructures are present in natural products offering a wide range of biological activities (Figure 1), such as tetrafibricin (nonpeptide fibrinogen receptor antagonist)[1] and muricapentocin (selective cytotoxicity for colon cancer cell line HT-29: ED_{50} 71 ng/mL),[2] as well as lydicamycin (antibiotic active against multidrug resistant strains),[3] sporminarin B (antifungal),[4] and amphidinol 3 (hemolytic and antifungal).[5]

Configurational assignments of isolated stereogenic centers in the 1,5-polyol sectors of these natural products present significant challenges, and in fact, many related compounds lack complete assignments of stereostructure.[2−4,6,7]

Application of aldol bond construction strategies[8] to 1,5-polyols would encounter daunting regio- and stereoselection problems in dehydration of alternating hydroxyl functions. New synthetic strategies tailored specifically for access to 1,5-polyols

(1) Isolation, structure, and biological activity: (a) Kamiyama, T.; Umino, T.; Fujisaki, N.; Fujimori, K.; Satoh, T.; Yamashita, Y.; Ohshima, S.; Watanabe, J.; Yokose, K. *J. Antibiot.* **1993**, *46*, 1039–1036. (b) Kobayashi, Y.; Czechtizky, W.; Kishi, Y. *Org. Lett.* **2003**, *5*, 93–96. (c) Satoh, T.; Kouns, W. C.; Yamashita, Y.; Kamiyama, T.; Steiner, B. *Biochem. J.* **1994**, *301*, 785–791. Synthetic studies: (d) Bouzbouz, S.; Cossy, J. *Org. Lett.* **2004**, *6*, 3469–3472. (e) Lira, R.; Roush, W. R. *Org. Lett.* **2007**, *9*, 533–536. (f) Zhang, K.; Curran, D. P. *Synlett* **2010**, 667–671.

(2) Kim, G.-S.; Zeng, L.; Alali, F.; Rogers, L. L.; Wu, F.-E.; McLaughlin, J. L.; Sastrodihardjo, S. *J. Nat. Prod.* **1998**, *61*, 432–436.

(3) Hayakawa, Y.; Kanamaru, N.; Morisaki, N.; Seto, H. *Tetrahedron Lett.* **1991**, *32*, 213–216. Tamotsu, F.; Keitaro, E.; Tomomitsu, S.; Hiroko, H.; Hirayasu, O.; Noriko, S.; Takeshi, F.; Hideo, N.; Yasuhiro, I. *J. Antibiot.* **2002**, *55*, 873–880.

(4) Mudur, S. V.; Gloer, J. B.; Wicklow, D. T. *J. Antibiot.* **2006**, *59*, 500–506.

(5) (a) Satake, M.; Murata, M.; Yasumoto, T.; Fujita, T.; Naoki, H. *J. Am. Chem. Soc.* **1991**, *113*, 9859–9861. (b) Murata, M.; Matsuoka, S.; Matsumori, N.; Paul, G. K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870–871. (c) Paquette, L. A.; Chang, S.-K. *Org. Lett.* **2005**, *7*, 3111–3114. (d) Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1411–1414. (e) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451–1454.

(6) Plaza, A.; Baker, H. L.; Bewley, C. A. *J. Nat. Prod.* **2008**, *71*, 473–477.

(7) A novel liposomal circular dichroism method has been devised to address the difficult structural analyses: MacMillan, J. B.; Molinski, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 9944–9945.

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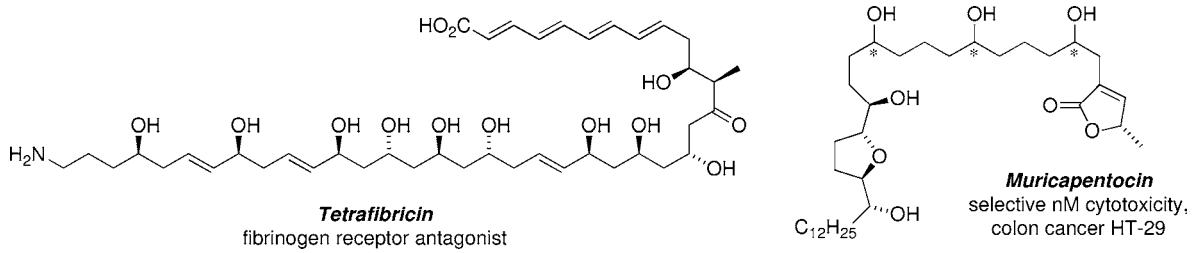


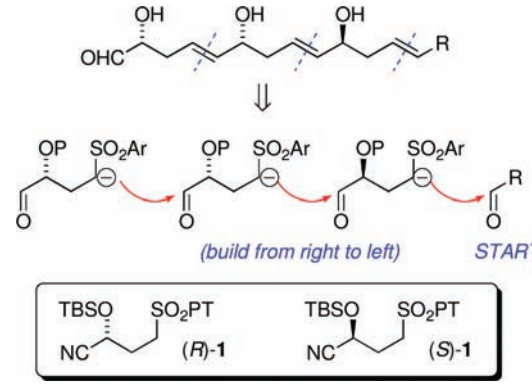
Figure 1. Structures of representative 1,5-polyol-containing bioactive natural products. Asterisks denote unknown configurations.

have attracted significant interest, leading to development of an iterative allylation and cross metathesis approach by Cossy et al.[9] and a bidirectional double allylboration by Roush et al.[10] These approaches to 1,5-polyols generate new stereogenic centers during C−C bond construction, which creates a number of configurational assignment problems, as the integrity of reagent control must be rigorously confirmed at each stage.

We sought a conceptually new approach to 1,5-polyols that would meet the following objectives: (a) carbon−carbon bond construction would occur without generating stereogenic centers, (b) preparation of all relative configurations would be equally facile, and (c) rapid assembly would be achieved with simple reagents. With these criteria in mind, we devised a configuration-encoded approach that defines the stereogenic center of each hydroxyl group within separate modules, prepared with both *R* and *S* configurations and designed for iterative assembly.[11] With hydroxyl configurations independent from the coupling chemistry, the desired configuration would be simply and unambiguously fixed during synthesis by the selection of building blocks at each stage of the iterative coupling sequence. This strategy-level innovation would not only permit versatile application to targets of known configurations but also facilitate stereochemical assignments of 1,5-polyol natural products through synthesis. Here, we report initial studies which validate this strategy and an application to a concise synthesis of the C27−C40 portion of tetrafibricin.

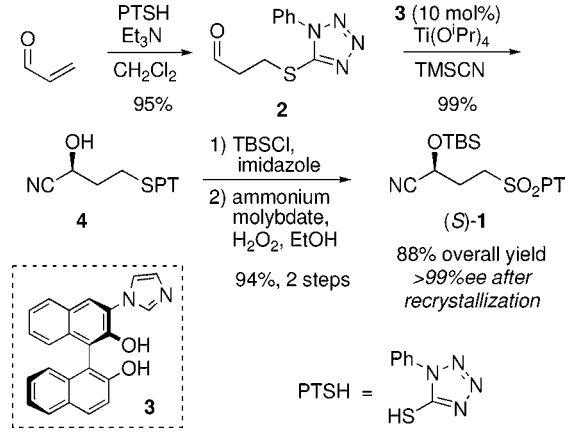
To initiate experimental efforts, we carefully selected a reliable method for the key C−C coupling which would link the configuration-encoded building blocks. We selected Julia−Kocienski olefination[12] as a well-established C−C bond construction that takes place under moderately basic conditions compatible with a wide range of functionalities. Accordingly, the four-carbon building block would need sulfone and aldehyde functionalities at the two termini, and oligomer synthesis would proceed via addition of the sulfone to the aldehyde functionality upon the growing 1,5-polyol chain (Scheme 1). The olefin functionality generated in this coupling could be retained or reduced, accommodating 1,5-polyol targets both saturated and unsaturated (Figure 1).

Scheme 1



Next, we identified a functional equivalent for the aldehyde, orthogonal to both O-silylprotection and Julia−Kocienski olefination. After some disappointing preliminary studies using protection of the aldehyde as an acetal, we turned to a nitrile as a masked aldehyde, to be revealed by DIBAL-H reduction. This called for preparation of α-silyloxy-γ-sulfononitrile **1** (Scheme 2).

Scheme 2



(8) Reviews: (a) Bode, S. E.; Wolberg, M.; Muller, M. *Synthesis* **2006**, 557–588. (b) Kimball, D. B.; Silks, L. A. *Curr. Org. Chem.* **2006**, *10*, 1975–1992.

(9) (a) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451–1454. (b) Also see ref 1d.

(10) (a) Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644–13645. (b) Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1411–1414. (c) Also see ref 1e.

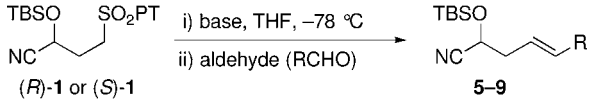
(11) Oishi, T.; Kanemoto, M.; Swasono, R.; Matsumori, N.; Murata, M. *Org. Lett.* **2008**, *10*, 5203–5206.

(12) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.

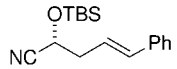
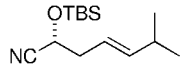
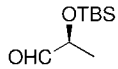
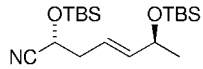
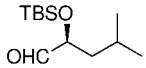
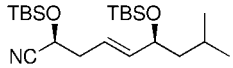
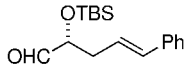
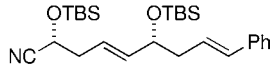
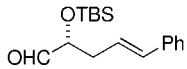
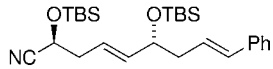
Synthesis of the configuration-encoded building blocks (*R*)-**1** and (*S*)-**1** (Scheme 2) commenced with addition of commercially available 1-phenyl-1*H*-tetrazol-5-thiol (PTSH) to acrolein to afford aldehyde **2**, which was then subjected to asymmetric addition of trimethylsilyl cyanide in the presence of catalyst **3**·Ti(O*i*-Pr)$_4$[13] to afford cyanohydrin **4** in 83−86% ee.[14] Without further optimization, the asymmetric cyanation on ca. 10 g scale afforded (*R*)-**4** (99% yield) and (*S*)-**4** (96% yield), with ligand recoveries of 92 and 71%, respectively. Protection of the hydroxyl group as a *tert*-butyldimethylsilyl ether and S-oxidation (H_2O_2, 4 mol % ammonium molybdate) furnished sulfone (*S*)-**1** in an overall yield of 88% from commercial materials. Recrystallization of (*R*)- or (*S*)-**1** furnished enantiopure material (60% recovery, one crop).

The initial Julia−Kocienski couplings (Table 1) of **1** were very clean and highly selective. Metalation of **1** (NaHMDS or KHMDS, −78 °C)[15] and coupling with a variety of aldehydes afforded the expected adducts (*E*/*Z* ratios from 95:5 to >98:2, Table 1).[16] With benzaldehyde, adduct **5** was obtained in 98% yield (*E*/*Z* > 98:2, entry 1). Aliphatic (entry 2) and α-silyloxy-substituted aliphatic aldehydes (entries 3−6) also coupled efficiently, regardless of whether 1,5-*syn* or 1,5-*anti* relative configurations were formed (entries 5 and 6).

Table 1. Julia−Kocienski Couplings of (*R*)-**1**[a]

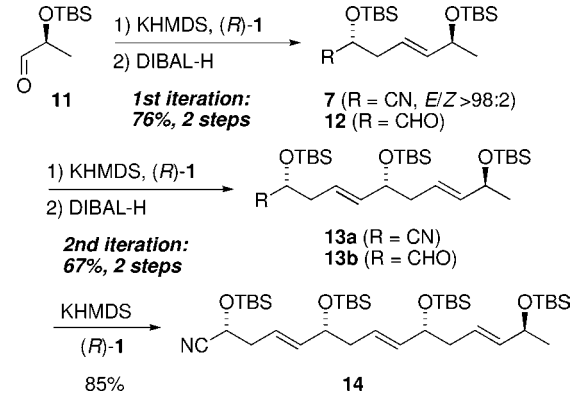


(*R*)-**1** or (*S*)-**1** — **5**–**9**

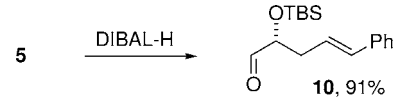
entry	aldehyde	sulfone	product, yield (ratio)
1[b]	PhCHO	(*R*)-**1**	 **5**, 99% (*E*/*Z* >98:2)[d]
2[c]	*i*-PrCHO	(*R*)-**1**	 **6**, 96% (*E*/*Z* 95:5)[d]
3[b]		(*R*)-**1**	 **7**, 95% (*E*/*Z* >98:2)[d]
4[b]		(*S*)-**1**	 **8**, 99% (*E*/*Z* >95:5)[e]
5[b]	 **10**	(*R*)-**1**	 (*R*,*R*)-**9**, 88% (*E*,*E*/*E*,*Z* >95:5)[e]
6[b]	 **10**	(*S*)-**1**	 (*S*,*R*)-**9**, 96% (*E*,*E*/*E*,*Z* >95:5)[e]

[a] Conditions: (*R*)-**1**, base (1.2 equiv, NaHMDS or KHMDS), −78 °C, 45 min; then aldehyde (1.0 equiv), −78 °C to ambient temperature, 3 h. [b] KHMDS was employed. [c] NaHMDS was employed. [d] *E*/*Z* ratio measured by integration of the ^{1}H NMR spectrum. [e] ^{1}H NMR peaks for the *Z* isomer were not observed.

Scheme 3



Next, the unveiling of the masked aldehyde was examined. Upon exposure to DIBAL-H, nitrile reduction of **5** smoothly released the aldehyde **10** in 91% yield (eq 1) for a second iteration of the coupling sequence. This completes one full iteration in overall 88% yield.



(1)

The iterative approach was next tested in three successive couplings of lactaldehyde **11** with (*R*)-**1**. The first iteration gave 1,5-diol **12** in 76% yield over two steps (*E*/*Z* > 98:2); a second iteration and third coupling afforded 1,5,9-triol **13** (67%, two steps) and 1,5,9,13-tetrol **14**, respectively. In the second and third couplings, minor *Z* isomers were not observed in ^{1}H NMR spectra; they presumably form in amounts less than 5% (by analogy with the first coupling).

Finally, we examined application of this strategy toward synthesis of the C27−C40 fragment of tetrafibricin, a nonpeptide fibrinogen receptor antagonist[17] inhibiting platelet aggregation by blocking glycoprotein interactions at the platelet surface. Tetrafibricin is the subject of ongoing synthetic efforts.[1] The most advanced route reported to date

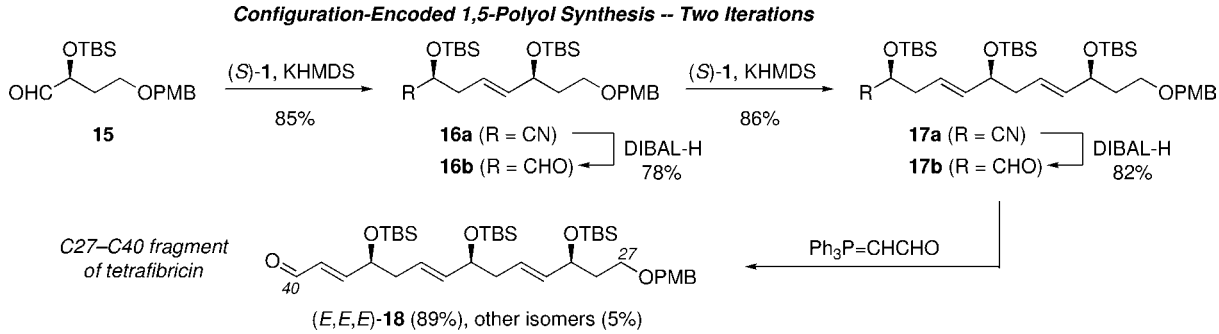
(13) Qin, Y. C.; Liu, L.; Pu, L. *Org. Lett.* **2005**, *7*, 2381–2383.

(14) Configurations were assigned via MPA esters: Louzao, I.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Commun.* **2006**, *142*, 2–1424.

(15) (a) A control experiment detected no loss of enantiopurity in (*R*)-**1** after treatment with NaHMDS in THF and quenching with water. (b) Use of NaHMDS in refluxing benzene for metallation of *O*-alkylcyanohydrin: Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275–1276. (c) To our knowledge, selective metallation and/or Julia coupling of a sulfone bearing remote *O*-alkyl- or *O*-silylcyanohydrin functionality has not been previously reported.

(16) Measurements of *E*/*Z* ratios were accomplished by integration of an ^{1}H NMR resonance attributed to an olefin proton of the minor *Z* isomer, appearing upfield of the major olefin protons. In cases where such a resonance could not be integrated (either not present or not resolved), the ratio was recorded in Table 1 as >95:5.

Scheme 4



is that of Curran, who reported syntheses of C1−C20 and C21−C40 fragments in 14 steps (2.2% yield) and 17 steps (2.6% yield), respectively; fragment coupling has not been reported.[1f,18]

From aldehyde **15**[19] (80% ee), we have prepared the C27−C40 fragment of tetrafibricin in five steps and 42% yield using two iterations of configuration-encoded Julia−Kocienski coupling (Scheme 4). Coupling in the first iteration gave **16a** (*E*/*Z* = 95:5, ^{1}H NMR), and then reduction of the nitrile function unveiled aldehyde **16b** (78% yield, plus 14% recovery of **16a**) for the second iteration. Another coupling with (*S*)-**1** and reduction afforded **17b**. Homologation with a stabilized ylide afforded α,*β*-unsaturated aldehyde **18**, isolated as a single isomer in 89% yield, completing the assembly of the C27−C40 carbon skeleton of tetrafibricin. In this last step, the small quantities of minor isomers (5% combined yield) indicated very high selectivities in all of the Julia−Kocienski olefinations en route to **18**, and by analogy, those shown in Scheme 3.

In conclusion, we have designed a concise and extremely efficient strategy for stereocontrolled synthesis of 1,5-polyols. The approach employs asymmetric catalysis to install the oxygen-bearing stereogenic centers, in contrast to existing approaches using stoichiometric chiral reagents. The key innovation in this 1,5-polyol synthesis is at the strategy level, encoding the hydroxyl configuration within a simple repeating unit that is efficiently and cheaply prepared via a scalable route. Using reliable Julia−Kocienski coupling, facile assembly of all stereochemical permutations of any given 1,5-polyol may be readily envisioned, with configurations programmed by selection of building blocks.

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Supporting Information Available: Preparative and characterization data for **1**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Satoh, T.; Kouns, W. C.; Yamashita, Y.; Kamiyama, T.; Steiner, B. *Biochem. J.* **1994**, *301*, 785–791.

(18) Gudipati, V. *Ph.D. Thesis*, University of Pittsburgh, 2008. We thank Professor Dennis Curran for providing a copy of this thesis.

(19) (a) Prepared from $PMBOCH_2CH_2CHO$ by asymmetric cyanation and reduction with DIBAL-H. See Supporting Information. (b) $PMBOCH_2CH_2CHO$: Oka, T.; Murai, A. *Tetrahedron* **1998**, *54*, 1–20. Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1997**, *62*, 5672–5673.