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Synthesis of Enantiopure Termini-Differentiated Heptane Stereotriads.[1] Application to Side Chain-Functionalized Tetrahydrofurans of IKD-8344

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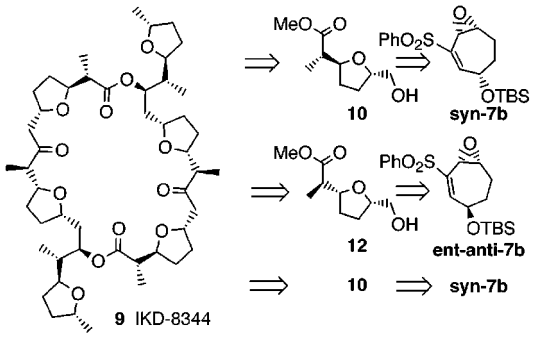
ABSTRACT



Enantiopure epoxy cycloheptenyl sulfones syn-7b and anti-7b are prepared in five high-yielding and stereospecific operations from 1,3-cycloheptadiene. These substrates serve as effective precursors for cis- and trans-substituted tetrahydrofurans (12, 10) which are segments of the antineoplastic agent IKD-8344.

We have begun a new research program which targets the efficient synthesis of optically pure termini-differentiated hexyl compounds (**1a**, $n = 6$) bearing up to four contiguous asymmetric centers.[2] The strategy features oxidative cleavage of cyclohexenyl triflates **2Ta** or vinyl sulfones **2Sa** as progenitors to the acyclic arrays **1a** (Figure 1). Establishment of the internal stereochemical relationships was dependent upon regio-, stereo-, and enantioselective functionalization of cross-conjugated dienyl triflates **3a** and dienyl sulfones **4a**. Absolute stereochemistry is readily introduced via Jacobsen catalytic epoxidation.[3]

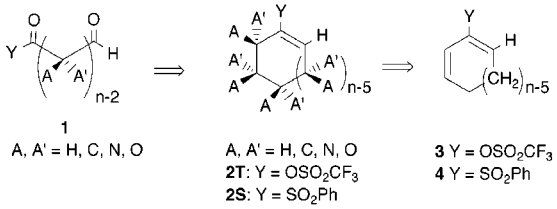


Figure 1. "a" series: $n = 6$; "b" series $n = 7$.

As we have previously demonstrated, compound **5b** and its enantiomer **ent-5b** can be prepared in ~80% yield with >95% enantioselectivity from 2-sulfonyl-1,3-cycloheptadiene

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(2) (a) Hentemann, M.; Fuchs, P. L. *Tetrahedron Lett.* **1999**, *40*, 2699. (b) Evarts, J. B., Jr.; Fuchs, P. L. *Tetrahedron Lett.* **1999**, *40*, 2703. (c) Hentemann, M.; Fuchs, P. L. *Org Lett.* **1999**, *1*, 355.

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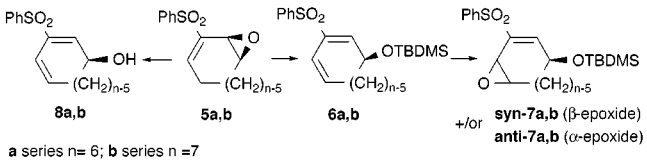
Table 1. Oxidation of Cycloheptadienyl Sulfones



no.	sm	reagents and conditions	prod(s)	yield (%) (ee)
1	**4b**	6% (*R,R*) Jacobsen cat., NaOCl, amine oxide, 0 °C, 6 h	**5b**	81 (95%)
2	**4b**	(*S,S*) Jacobsen cat., as above	**ent-5b**	79 (95%)
3	**5b**	1a, LiHMDS; 1b, TBDMSCl	**6b**	96
4	**5b**	1a, LiHMDS; 1b, NH_4Cl	**8b**	99
5	**6a**	TFA cat./Oxone, MeCN, 0 °C, 30 min	**s/a-7a**	1/4; 88%[2c]
6	**6b**	TFA cat./Oxone, MeCN, 0 °C, 30 min	**s/a-7b**	47/46
7	**6b**	mCPBA, CH_2Cl_2, 25 °C, 2 h	**s/a-7b**	56/34
8	**6b**	8% (*R,R*) Jacobsen cat., NaOCl, amine oxide, 0 °C, 10 h	**s/a-7b**	7/85 (>97%)
9	**6b**	(*S,S*) Jacobsen cat., as above	**s/a-7b**	85/7 (>98%)

(entries 1 and 2, Table 1).[4] Treatment of epoxyvinyl sulfone **5b** with LiHMDS generates sulfonyl-substituted silyl ether **6b** or dienylic alcohols **8b** depending upon whether the reaction is quenched with TBDMS-Cl or water (entries 3and 4, Table 1). *The cyclohexenyl and cycloheptenyl compounds fundamentally differ with respect to stereochemical control in subsequent epoxidation reactions.* While cyclohexadienyl silyl ether **6a** affords anti epoxy silyl ether **anti-7a** with excellent substrate-mediated selectivity, similar selectivity is not obtained with either the seven-membered silyl ether **6b** or alcohol **8b**.

In the case of silyl ether **6b**, both achiral reagents generate mixtures of the syn and anti epoxides **s/a-7b** (entries 6 and 7, Table 1). This stereochemical problem was solved by reagent-based double stereoselection via hypochlorite epoxidation of silyl ether **6b** in the presence of the enantiopure Jacobsen catalysts to provide epoxides **syn-7b** and **anti-7b** with ~12:1 selectivity (entries 8 and 9, Table 1). Chromatography or crystallization of these mixtures provided pure diastereomers in >75% yield and >97%ee. By comparison, epoxidation of the free alcohol **8b** was far more complicated. Oxidation of the allylic alcohol moiety of **8b** to enone occurred at competitive rates to epoxidation of the olefin, rendering the process inefficient (see Supporting Information).

The simplicity and high yields of the five-operation syntheses of **syn-7b** and **anti-7b** provide an excellent pair of intermediates for further modification.

In addition to using the cyclic vinyl sulfones as direct precursors of termini-differentiated acyclic heptyl fragments analogous to the hexyl compounds, these materials can also serve as precursors of *side chain-functionalized monocyclic intermediates*. For example, IKD-8344 **9** (Figure 2) is a C_2

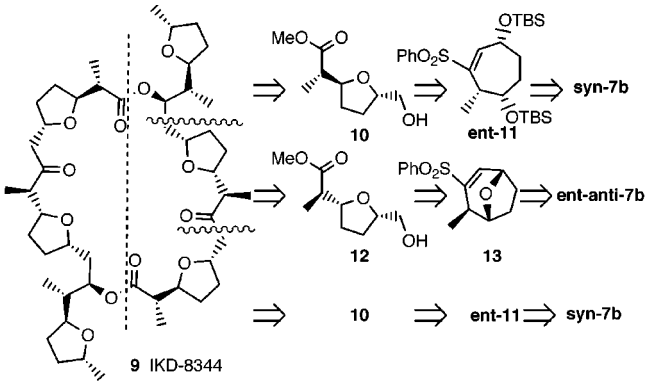


Figure 2.

symmetric 28-membered ring diolide which appears to have potential as an anticancer agent.[5] The secoacid segments of **9** can be envisioned to arise from one molecule of the enantiomer of enantiopure **anti-7b** and two molecules of **syn-7b**.

Access to the two key intermediates for preparation of IKD-8344 required development of new methodology for the stereoselective introduction of the pendant methyl groups. S_N2' methylation of **syn-7b** and **anti-7b** proved especially informative. For example, **ent-syn-7b** can be efficiently transformed to either key intermediate *all-syn* **11** or its *anti-syn* diastereomer **14** (relevant X-ray in Supporting Information), respectively (Figure 3). Similar reactions on **ent-anti-7b** serve to generate alcohol **16**, but under the stronger Lewis acid conditions **15** is not produced. Access to **15** was secured via Mitsunobu inversion[6] of **11**. The product formed in the trimethylaluminum (or HF) reaction with **ent-anti-7b** is bridged tetrahydrofuran **18**.

The regiochemistry of intramolecular oxygen alkylation of epoxide **ent-anti-7b** to **18** initially appears surprising, since one might have expected the compound to suffer attack at the allylically activated bond to afford **iso-18**. Molecular mechanics reveals that backside access to both carbons of the epoxide moiety is feasable. Energy calculations do not substantially favor one 6/5 ring system over the other. Bidentate coordination of the acid catalyst with *both the epoxide and the sulfonyl oxygen* may provide a rationale for the observed regioselectivity. As the reaction proceeds to form **18**, two-point bonding of the acid is maintained throughout, while opening to **iso-18** requires disruption of

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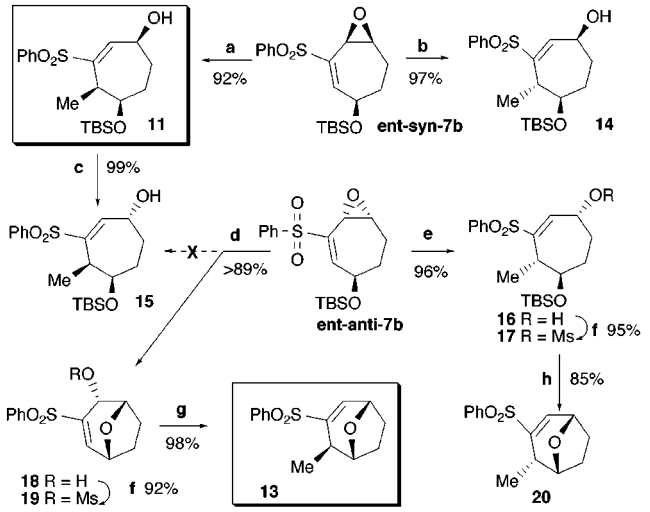

Figure 3.

the chelated activating function, presumably with a large enthalpic penalty (Figure 4).

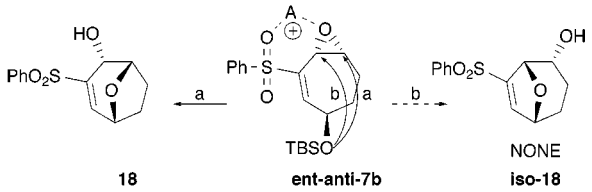

Figure 4.

Further conversion of **18** (99% ee by chiral HPLC) to mesylate **19** (relevant X-ray in Supporting Information) followed by reaction with dimethylcuprate[7] provided the desired bridged tetrahydrofuran **13**. Chiral HPLC analysis revealed that **13** had undergone substantial racemization (27−54% ee). Additional studies (Table 2) showed that omitting the HMPA decreased the racemization (55−73% ee), but the yield fell to 61%, suggestive of the intervention of a π-allyl copper intermediate. Fortunately, treatment of **19** with either trimethyl zincate[8a] or tetramethyl alanate[8b] provided the desired material with perfect fidelity. Further adjustment of conditions allowed the alanate reaction to deliver a quantitative yield of compound **13**.

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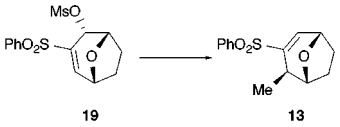
(8) (a) Tückmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581. (b) Inghardt, T.; Frejd, T.; Magnusson, G. *J. Org. Chem.* **1988**, *53*, 4542.

Table 2. Reagents, Reaction Conditions, and Results for S_N2' Methylation of **19**



no.	reagent	conditions	yield (%)	ee (%)
1	Me_2CuLi (1 equiv)	THF, 0.009 M, −78−10 °C 6 h, 23 °C 3 h	61	55
2	Me_2CuLi (1 equiv)	THF, 0.009 M, −78∼0 °C 6 h, 0 °C 6 h	61	73
3	Me_2CuLi (1 equiv)	THF, 2 equiv of HMPA, 0.009 M, −78 °C 10 h	88	54
4	Me_2CuLi (1 equiv)	THF, 4 equiv of HMPA, 0.009 M, −78 °C 10 h	88	27
5	Me_3ZnLi (1 equiv)	THF, 0.009 M, −78 °C 5 h	81	>99
6	Me_3ZnLi (1 equiv)	CH_2Cl_2, 0.09 M, −78−23 °C 8 h, 23 °C 6 h	80	>99
7	Me_4AlLi (1 equiv)	THF, 0.009 M, 23 °C 3 h	82	>98
8	Me_4AlLi (1 equiv)	CH_2Cl_2, 0.13 M, −78−23 °C overnight	98	>99

The alternate bridged tetrahydrofuran **20** is prepared from mesylate **17**. Both sequences are high yielding and stereoselective. Thus, **syn-7b** and **anti-7b** have served to generate a useful collection of seven-membered-ring stereotriads (Figure 3).

On the basis of our previous ozonolytic cleavage of six-membered-ring vinyl sulfones,[2c] we expected little difficulty in the conversion of **13** or **20** to the corresponding aldehyde−esters. However, our initial attempts at ozonolysis of these oxabicyclics were unrewarding, and the report by Bäckvall of failure on the desmethyl analogue[9] prompted us to adopt alternative cleavage methods. We employed catalytic osmium tetroxide for conversion of **13** to α-hydroxyketone **21** but only obtained about 58% yield which was comparable to the yield in Bäckvall's desmethyl substrate.[8] Reaction of **13** with catalytic ruthenium dioxide[10] and 2 equiv of periodate (added in three portions) raised the yield of **21** to 90%. Alternatively, use of 3 equiv of periodate in the ruthenium dioxide reaction directly gave carboxylic acid **22** in 89%. Treatment of **22** with 1,3-(dicyclohexyl)methylisourea[11] then afforded ester **23**. Isolation of acid **22** can be avoided by effecting the oxidation of **21** with lead tetraacetate in methanol,[12] directly providing ester **23** in 94% yield. Completion of the synthesis of segment **12** is achieved in 98% yield by reduction of the aldehyde with $LiAlH(Ot\text{-}Bu)_3$ (Figure 5). Compound **12** was previously prepared a number

(9) Lofstrom, C. M. G.; Ericsson, A. M.; Bourrinet, L.; Juntunen, S. K.; Bäckvall, J.-E. *J. Org. Chem.* **1995**, *60*, 3586. We have subsequently developed a successful ozonolytic cleavage of **13** and **20** which also smoothly cleaves the desmethyl Bäckvall substrate. This subject will be discussed in a future publication. We wish to thank Professor Bäckvall for useful discussions about this transformation.

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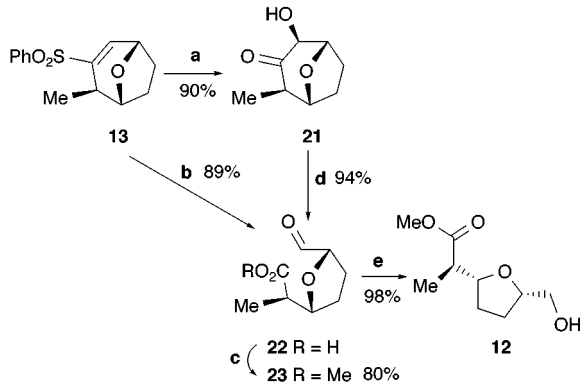
(12) Rodriguez, J. R.; Rumbo, A.; Castedo, L.; Mascarenas, J. L. *J. Org. Chem.* **1999**, *64*, 4560. (b) Baer, E. *J. Am. Chem. Soc.* **1942**, *64*, 1416.



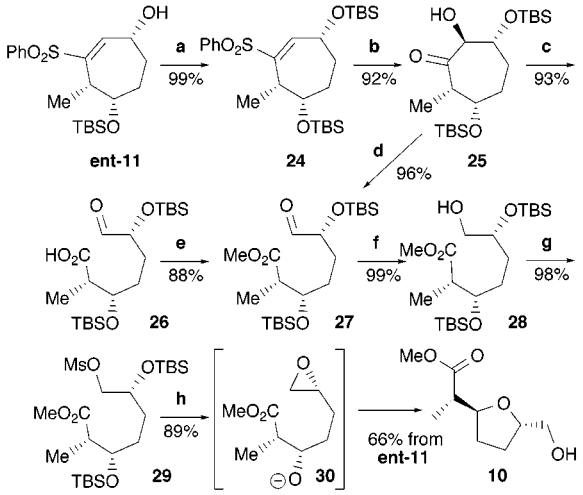
a. RuO_2 0.03eq, $NaIO_4$ 2 eq (3 portions); $CCl_4/CH_3CN/H_2O$ 1:1:1.5 pH=5, 23°C, 30min; **b.** RuO_2 0.03eq, $NaIO_4$ 3 eq ; $CCl_4/CH_3CN/H_2O$ 1:1:1.5 pH=5, 23°C, 1h; **c.** CyNHC(OMe)=NCy, THF, 23°C, 1.5d; **d.** $Pb(OAc)_4$, 1.5 eq, MeOH, 23°C, 1h; **e.** $LiAlH(O\text{-}tBu)_3$, THF, 1eq, 0°C, 2h

Figure 5.

of times since it is an intermediate in the synthesis of the C_2 symmetric macrocyclic lactone antibiotic nonactin. The best previous synthesis of this material starts with *l*-glutamic acid and affords **12** in six operations and 25% overall yield.[13] Our synthesis has nine operations in 44% overall yield (average yield 91% per operation).

Silylation of **ent-11** provided bis TBS ether **24** which was stereospecifically converted to α-hydroxyketone **25** by the general method of Bäckvall.[8] Oxidative cleavage of **25** with periodate followed by esterification of carboxylic acid **26** with 1,3-(dicyclohexyl)methylisourea[11] gave methyl ester−aldehyde **27** without difficulty. Application of the lead tetraacetate/methanol procedure[12] again obviated the necessity of isolating carboxylic acid **26**. Selective reduction of the aldehyde moiety of **27** smoothly provided alcohol **28** which was directly transformed to mesylate **29**. Reaction of **29** with 2.2 equiv of tetrabutylammonium fluoride in the presence of 4 Å molecular sieves (crucially important) presumably proceeded via an intramolecular 5-exo cyclization[14] of epoxide intermediate **30** which provided the previously unknown *trans*-fused tetrahydrofuran **10**. The synthesis of **10** required 10 operations and was accomplished in 45% overall yield (average yield 92% per operation, Figure 6). Conversion of these segments to IKD-8344 **9** will be reported in due course.

(13) Batmangherlich, S.; Davidson, A. H. *Chem. Commun.* **1985**, 1399.



a. TBSCl, imidazole, DMAP cat., CH_2Cl_2, 23°C; **b.** OsO_4 0.05eq NMO 3eq, acetone/H_2O(2/1) 23°C, 8h; **c.** $NaIO_4$ 2.5eq, t-BuOH/H_2O(2/1) 23°C, 8-10h; **d.** $Pb(OAc)_4$, 1.1 eq, MeOH, 23°C, 2h; **e.** CyNHC(OMe)=NCy, THF, 23°C; **f.** $LiAlH(O\text{-}t\text{-}Bu)_3$ 1eq, THF, -78°C, 4h; **g.** MsCl 1eq, Et_3N 1eq, CH_2Cl_2, 0°C, 0.5h; **h.** TBAF 2.2eq, 4Å MS, THF, 23°C, 4h

Figure 6.

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Supporting Information Available: Representative experimental procedures, X-ray structure data for **ent-14** and **ent-19**, and ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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