Pergamon

Tetrahedron Letters 41 (2000) 7795–7799

TETRAHEDRON LETTERS

Synthesis and oxidation reactions of cycloheptatrienyl sulfones

Zhiwei Tong, Yuzhong Chen, Martin F. Hentemann and Philip L. Fuchs*

Department of Chemistry, Purdue University, West Lafayette, IN 47907, USA

Received 8 August 2000; accepted 14 August 2000

Abstract

Inexpensive cycloheptatriene is regiospecifically converted to all three phenylsulfonyl substituted cycloheptatrienes. Epoxidation of these materials with achiral reagents is shown to be relatively regiospecific. Reasonable levels of enantiomeric excess ($\sim$63,78%) are achieved by Sharpless asymmetric dihydroxylation of a pair of 3-substituted trienes. Crystallization of these sulfones provides the diols in enantiomeric excesses greater than 90%. © 2000 Published by Elsevier Science Ltd.

Multiply convergent synthetic strategies place high value upon efficient construction of assemblies such as **1**, which are typically employed as sub-goals as a prelude to assembly of the final target. We are currently exploring the synthesis of optically pure termini-differentiated hexyl (**1a**, $n=6$) and heptyl (**1b**, $n=7$) compounds bearing up to five contiguous chiral centers (Fig. 1).[1]

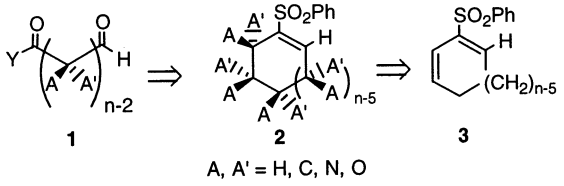


Figure 1.

Preparation of the full family of prochiral trienyl sulfones from inexpensive cycloheptatriene is of general significance since these materials may now be examined as starting materials for a variety of potentially enantiospecific cycloaddition and conjugate–addition/alkylation reactions. For example, we speculated that trienyl sulfones such as **4** might serve as substrates for a sequence of nucleophilic and electrophilic functionalizations which ultimately afford generic

* Corresponding author. Tel: +1 765 494 5242; fax: +1 765 494 7679; e-mail: pfuchs@purdue.edu

0040-4039/00/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0040-4039(00)01386-1

sulfone **5** after elimination of a molecule of HE_3. Completion of the hypothetical synthesis would then involve oxidative scission of the vinyl sulfone functionality to deliver substrate **6** appropriately functionalized for further connective operations. Clearly, such an approach raises a myriad of enantio-, stereo-, regio-, and chemoselectivity questions, but before these can be addressed, effective access to this unknown class of compounds needed to be achieved (Fig. 2).

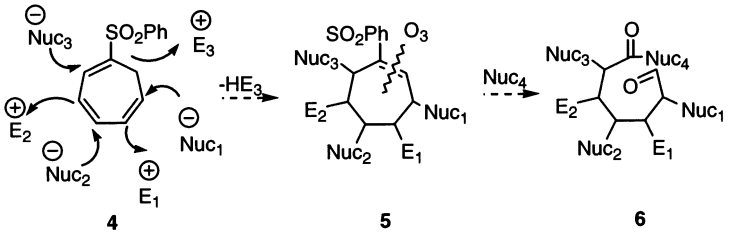


Figure 2.

Cycloheptatriene **7** is an ideal substrate for synthesis of multiply-functionalized 7-membered ring vinylsulfones because of its insignificant cost and high oxidation state.[2] Reaction of **7** with phenylsulfenylchloride, prepared in situ from thiophenol and *N*-chlorosuccinimide,[3] afforded a mixture of adducts which were not separated, but directly oxidized to the chlorosulfones and treated with triethylamine to converge to 1-substituted trienylsulfone **4** as a single regioisomer in 68% overall yield (Fig. 3).

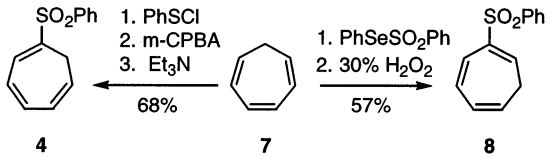


Figure 3.

Synthesis of the 2-substituted triene **8** in 57% overall yield was accomplished by addition of the Back phenylselenylsulfonate reagent[4] to cycloheptatriene **7** followed by oxidation and elimination with hydrogen peroxide. Synthesis of the 3-substituted triene **12** was more difficult. Treatment of cycloheptatriene **7** to generate tropylium fluoroborate[5] followed by addition of thiophenol provided 7-thiophenyl cycloheptatriene **9**[6] in 71% yield. Thermal rearrangement of 0.05 M triene **9** with 0.05 equiv. hydroquinone in benzene at 185°C for 1 h (sealed tube) provided 3-thiophenyl-cycloheptatriene **10** in a modest 46% yield along with 43% recovered **10**. Extending the reaction time to 19 h delivers 1-thiophenyl-cycloheptatriene **11** in 41% along with 19% recovered **9**, but only traces of **10** remain. Relative R_f values (SiO_2–100% hexane) for **9**, **10**, and **11** are 0.25, 0.49, and 0.51, respectively, which allows ready separation of **9** and **10**. Oxidation of **10** gives the requisite sulfone **12** in 89% yield (Fig. 4).

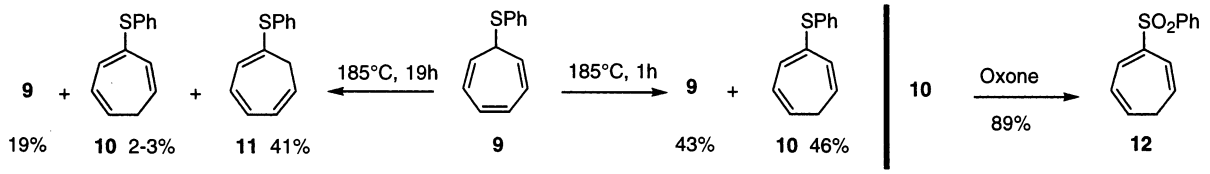
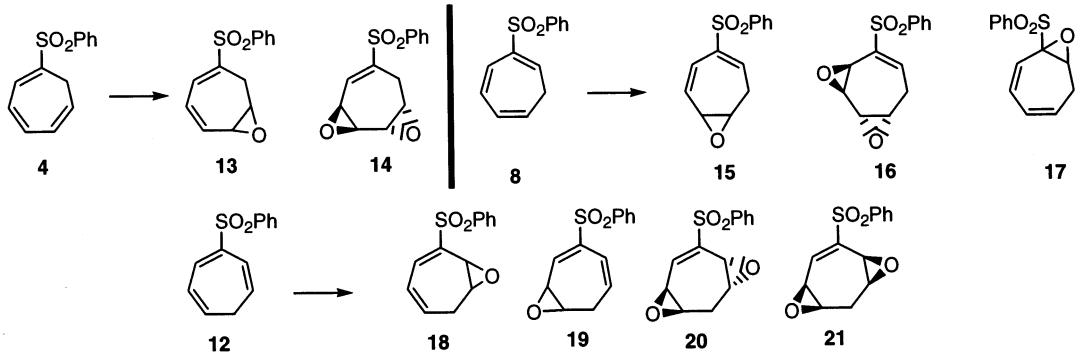


Figure 4.

Epoxidation of the three cycloheptenyl sulfones was evaluated using both achiral and chiral reagents. The trienyl substrates were substantially less reactive than the parent 2-phenylsulfonyl-cyclohepta-1,3-diene **3b**. While **3b** is a premier substrate for Jacobsen epoxidation,[1c] it is clear from Table 1 that addition of the third double bond deactivates the substrate and serves to decrease the facial specificity, presumably due to resonance-related flattening of the cycloheptatriene ring (Table 1).

Table 1
Achiral and Jacobsen epoxidations[a]



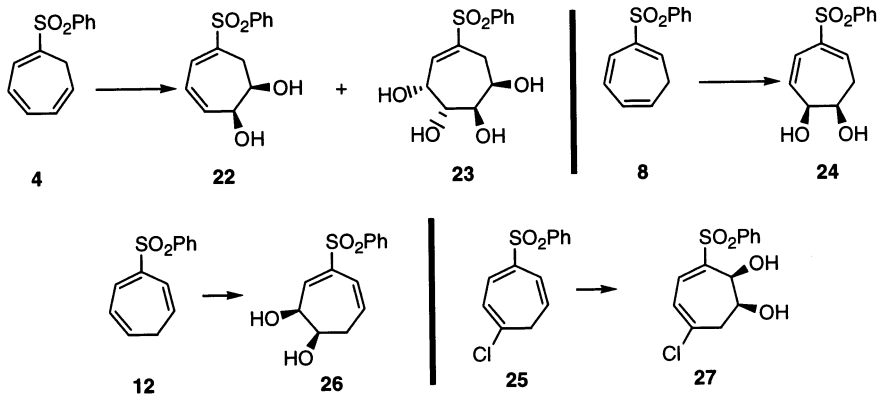
SM	Conditions	Product(s)	Yield (%)	SM	Conditions	Product(s)	Yield (%)
4	**A**	**13**	40 (41% ee)	**4**	**E**	**13**:**14** (2.3:1)	75
4	**B**	**13**	40 (37% ee)	**4**	**D**	**13**	23
4	**C**	**13**	38	**8**	**A**	**15**	28
8	**B**	**15**	33	**8**	**F**	**15**	85
8	**G**	**16**	87	**8**	**H**	**17**	65
8	**I**	**17**	95	**12**	**A**	–	12 recovered
12	**B**	–	12 recovered	**12**	**J**	**18**:**20** (1.3:1)	89
12	**E**	**20**:**21** (12:1)	85	**12**	**C**	**18**:**19** (2:1)	10

[a] Conditions: **A**: (*R*,*R*)-Jac. cat. (0.08 equiv.), P_3NO (0.32 equiv.), 12% bleach (3 equiv.), MC, 0°C, 5 h; **B**: (*S*,*S*)-Jac. cat. (0.08 equiv.), P_3NO (0.32 equiv.), 12% bleach (3 equiv.), MC, 0°C, 5 h; **C**: (*R*,*R*)-Jac. cat. (0.2 equiv.), NH_4OAc (0.25 equiv.), 30% H_2O_2 (3 equiv.), MC–MeOH (1:1), 0°C, 6 h; **D**: (*S*,*S*)-Jac. cat. (0.2 equiv.), NH_4OAc (0.25 equiv.), 30% H_2O_2 (3 equiv.), MC–MeOH (1:1), 0°C, 6 h; **E**: Na_2EDTA (0.003 equiv.), trifluoroacetone (10 equiv.), Oxone® (7.8 equiv.), $NaHCO_3$ (5 equiv.), MeCN, 0°C, 1 h; **F**: *m*-CPBA (2.5 equiv.), MC, rt, 28 h; **G**: Na_2EDTA (0.003 equiv.), trifluoroacetone (10 equiv.), Oxone® (7.8 equiv.), $NaHCO_3$ (5 equiv.), MeCN, 0°C, 0.5 h; **H**: 30% H_2O_2 (5 equiv.), NaOH (1 equiv.), MeOH; **I**: *n*-BuLi (1.2 equiv.), *t*-BuOOH (1.5 equiv.), THF, −40°C, 3 h; **J**: *m*-CPBA (2.5 equiv.), MC, rt, 12 h; 0°C, 7 h.

Sharpless asymmetric dihydroxylation of trienyl sulfones **4** and **8** was also disappointing. In contrast, although slow, reaction of **12** and **25** provided reasonable levels of asymmetric induction. In fact, one recrystallization of diol **27** served to remove crystalline racemic material providing **27** with >90% ee as the 'crystallization residue' (Table 2).

Synthesis of chlorinated trienylsulfone **25** was accomplished by treatment of cycloheptane-1,3-dione **28**[7] with oxalyl chloride to give vinylogous acid halide **29**. Bis-sulfenylation of **29** with phenylsulfenyl chloride in THF afforded thioacetal **30** in 70% yield. DIBAl-H reduction of **30** smoothly provided allylic alcohol **31** in near-quantitative yield. Compound **31** is thus conveniently prepared on a 25 g scale.

Table 2
Sharpless dihydroxylation[a]



SM	Reaction time (h)	Product(s)	Yield (%)	ee (%)
4	46	**22**:**23** (4:1)	75	36
8	46	**24**	73	38
12	10	**26**	51	63
25	120	**27**	45[b]	78

[a] Conditions: $(DHQ)_2PHAL$ (0.1 equiv.) or $(DHQD)_2PHAL$ (0.1 equiv.), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.), OsO_4 (0.1 equiv.), $MeSO_2NH_2$ (3 equiv.), *t*-BuOH/H_2O, 0°C.
[b] Based upon recovered starting material; 18% absolute yield, $(DHQ)_2PHAL$ as ligand.

The key reaction in this sequence is the reaction of **31** with three equivalents of *m*-CPBA which provides vinylsulfone **32**, presumably regiospecific via loss of sulfinic acid from the α-sulfinylsulfone intermediate. Treatment of alcohol **32** with mesyl chloride in the presence of excess triethylamine effects 1,4-elimination to chloro-substituted triene **25**[8] as a single regioisomer. This specificity results from the inductive acidification of the sulfone-bearing γ-hydrogen (Fig. 5).

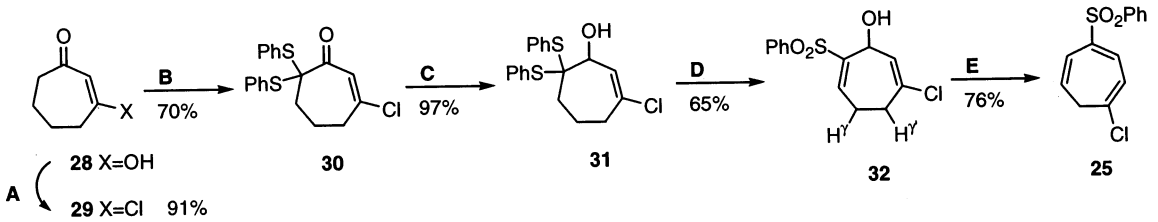


Figure 5. Conditions: **A**: $(COCl)_2$ (1.2 equiv.), $CHCl_3$, rt, 5 h; **B**: PhSCl (2.2 equiv.), THF–HMPA (10:1), 0°C, 2 h; **C**: DIBAl-H (1.5 equiv.), MC. −78°C, 2 h; **D**: *m*-CPBA, MC, rt, 1 h; **E**: MsCl (1.5 equiv.), Et_3N (3 equiv.), MC, 0°C, 0.5 h

Acknowledgements

We acknowledge Arlene Rothwell and Karl Wood for mass spectral data and the NIH for partial support of this project (GM# 32693).

References

1. Synthesis Via Vinyl Sulfones **83**. Chiral Carbon Catalog **6**; for earlier papers in the latter series see: (a) Hentemann, M.; Fuchs, P. L *Tetrahedron Lett*. **1999**, *40*, 2699; (b) Evarts Jr., J. B.; Fuchs, P. L. *Tetrahedron Lett*. **1999**, *40*, 2703; (c) Hentemann, M.; Fuchs, P. L. *Org. Lett*. **1999**, *1*, 355.
2. Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Cuisiat, S. V.; Ferguson, M. D.; Henshwood, J. A.; Krueger, A. C.; Ogbu, C. O.; Short, K. M.; Heeg, M. J. *J. Am. Chem. Soc*. **1993**, *115*, 1382; (b) Paquette, L. A.; Kang, H.-J.; Ra, C. S. *J. Am. Chem. Soc*. **1992**, *114*, 7387; (c) Johnson, C. R. *Acc. Chem. Res*. **1998**, *31*, 333; (d) Johnson, C. R.; Golebiowski, A.; Steensma, D. H.; Scialdone, M. A. *J. Org. Chem*. **1993**, *58*, 7185; (e) Pearson, A. J.; Srinivasan, K. *J. Org. Chem*. **1992**, *57*, 3965; (f) Lautens, M.; Ren, Y.; Delanghe, P.; Chiu, P.; Ma, S.; Colucci, J. *Can. J. Chem*. **1995**, *73*, 1251.
3. Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem*. **1978**, *43*, 1208.
4. Back, T. G.; Collins, S. *Tetrahedron Lett*. **1980**, *21*, 2213; (b) Back, T. G.; Lai, E. K. Y.; Muralidharan, K. R. *Tetrahedron Lett*. **1989**, *30*, 6481; (c) Bäckvall, J.-E.; Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev*. **1998**, *98*, 2291; (d) Backvall, J.-E.; Juntunen, S. K. *J. Org. Chem*. **1988**, *53*, 2398; (e) Backvall, J.-E.; Juntunen, S. K.; Andell, O. S. *Org. Synth*. **1990**, *68*, 148; (f) Backvall, J.-E.; Ericsson, A. M.; Juntunen, S. K. *J. Org. Chem*. **1993**, *58*, 5221; (g) Backvall, J.-E.; Najera, C.; Yus, M. *Tetrahedron Lett*. **1988**, *29*, 1445. (h) Lin, H. S.; Coghlan, M. J.; Paquette, L. A. *Org. Synth*. **1988**, *67*, 157.
5. Conrow, W. *Org. Synth*. **1973**, *Col. Vol. 5*, 1138.
6. Cavazza, M.; Morganti, G.; Pietra, F. *J. Org. Chem*. **1980**, *45*, 2001.
7. Ragan, J. A.; Makowski, T. W.; am Emde, D. J.; Clifford, P. J.; Young, G. R.; Conrad, A. K.; Eisenbeis, S. A. *Org. Process Res. Dev*. **1998**, *2*, 379.
8. **1-Benzenesulfonyl-1,3,5-cycloheptatriene (4)**: ^{1}H NMR (500 MHz, $CDCl_3$): 7.91–7.94 (m, 2H), 7.51–7.64 (m, 3H), 7.26 (d, $J=0.48$ Hz, 1H), 6.76 (q, $J=5.62$ Hz, 1H), 6.62–6.66 (m, 1H), 6.21 (dd, $J=5.62$ and 9.52 Hz, 1H), 5.33–5.38 (m, $J=0.49$, 6.84, and 9.52 Hz, 1H), and 2.59 (d, $J=6.84$ Hz, 2H); **2-benzenesulfonyl-1,3,5-cycloheptatriene (8)**: ^{1}H NMR (500 MHz, $CDCl_3$): 7.75–7.79 (m, 2H), 7.44–7.59 (m, 3H), 6.84 (dt, $J=0.46$ and 11.44 Hz, 1H), 6.71–6.79 (m, $J=5.49$, 5.65 and 11.44 Hz, 1H), 6.48 (td, $J=0.46$ and 7.44, 1H), 6.13 (dd, $J=5.49$ and 9.46 Hz, 1H), 5.46 (dt, $J=6.57$ and 9.46 Hz, 1H), and 2.41 (dd, $J=6.87$ and 7.17 Hz, 2H); **3-benzenesulfonyl-1,3,5-cycloheptatriene (12)**: ^{1}H NMR (300 MHz, $CDCl_3$): 7.91–7.95 (m, 2H), 7.73 (d, $J=6.87$ Hz, 1H), 7.55–7.58 (m, 3H), 6.53 (d, $J=9.61$ Hz, 1H), 6.37 (dd, $J=5.96$ and 9.31 Hz, 1H), 5.62 (dt, $J=6.87$ and 9.31 Hz, 1H), 5.43 (dt, $J=6.87$ and 9.61 Hz, 1H), and 2.25 (t, $J=6.87$, 2H); **5,6-epoxy-2-benzenesulfonyl-1,3-cycloheptadiene (15)**: ^{1}H NMR (500 MHz, $CDCl_3$): 7.85–7.89 (m, 2H), 7.09 (t, 1H), 7.49–7.63 (m, 3H), 3.53–3.57 (m, 1H), 6.17–6.27 (m, $J=5.62$ and 11.72 Hz, 2H), 3.09 (dt, $J=3.18$ and 3.42 Hz, 1H), 2.93 (ddd, $J=2.93$, 5.62 and 14.89 Hz, 1H), and 2.65 (ddd, $J=5.62$, 7.57 and 14.77 Hz, 1H); **5,6-dihydroxyl-1-benzenesulfonyl-1,3-cycloheptadiene (22)**: ^{1}H NMR (500 MHz, $CDCl_3$): 7.84–7.88 (m, 2H), 7.50–7.64 (m, 3H), 7.16 (dt, $J=3.51$ Hz, 1H), 6.08 (q, 2H), 4.31–4.33 (m, 1H), 3.95–4.00 (m, 1H), 2.65 (dd, $J=0.92$ and 6.41 Hz, 2H), and 2.24 (s, br, –OH); **5,6-dihdroxyl-2-benzenesulfonyl-1,3-cycloheptadiene (24)**: ^{1}H NMR (500 MHz, $CDCl_3$): 7.83–7.89 (m, 2H), 7.50–7.65 (m, 3H), 7.26 (t, 1H), 6.18 (d, 1H), 5.97 (dd, 1H), 4.77 (s, br, –OH), 4.25 (s, br, 1H), 4.08–4.14 (m, 1H), 2.71 (t, 2H); **1-chloro-4-benzenesulfonyl-cyclohepta-1,3,5-triene (25)**: ^{1}H NMR (300 MHz, $CDCl_3$): 7.88–7.92 (m, 2H), 7.52–7.63 (m, 4H), 6.61 (d, $J=9.3$ Hz, 1H), 6.54 (d, $J=6.6$ Hz, 1H), 5.65 (dt, $J=9.3$, 6.9 Hz, 1H), and 2.76 (d, $J=6.9$ Hz, 2H). **1-chloro-4-benzenesulfonyl-5,6-dihydroxy-cyclohepta-1,3-diene (27)**: ^{1}H NMR (300 MHz, C_6D_6): 7.90–7.96 (m, 2H), 7.10–7.15 (m, 3H), 7.01 (d, $J=8.7$ Hz, 1H), 5.81 (dd, $J=2.7$, 8.7 Hz, 1H), 4.85 (br s, 1H), 3.93 (br s, 1H), 3.59 (br d, $J=11.1$ Hz, 1H), 3.32 (ddd, $J=2.7$, 11.1, 18.3 Hz, 1H), 3.05 (br s, 1H), 2.63 (br d, $J=18.3$ Hz, 1H).