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Investigation of the Diastereoselective Cyclization of Bis-sulfonyl Esters

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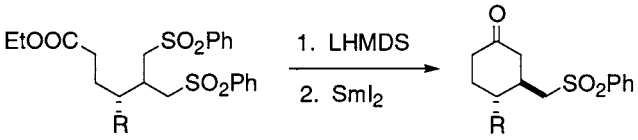
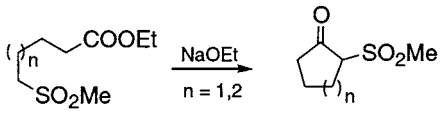
ABSTRACT



The diastereoselective cyclization of bissulfonyl esters was investigated by varying both the size and the placement of the substituent on the tether adjoining the reacting centers. Substitution at either the α or *β* position relative to the ester moiety gave diastereomeric ratios of (1–3):1, while *γ* substitution dramatically increased the diastereomeric ratios to (6–20):1.

The formation of cyclohexanones containing several stereocenters has been a challenging problem in organic synthesis, and many elegant solutions have been developed over the years. A few examples include the Diels−Alder reaction,[1] anisole manipulation,[2] and intramolecular ene reaction[3] followed by oxidation. We would like to introduce a novel approach to cycloalkanones containing several stereocenters based on the well-known Claisen condensation of sulfones with esters. As shown in Scheme 1, Truce[4] introduced the

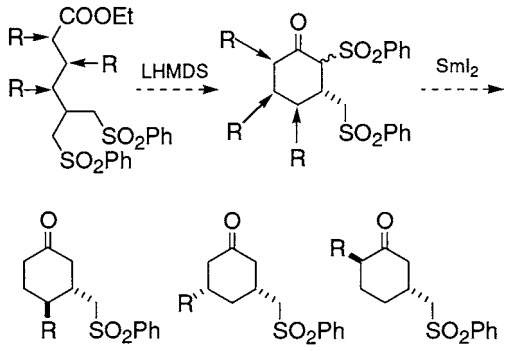
Scheme 1



intramolecular cyclization of sulfonyl esters to produce cyclopentanones and cyclohexanones, which Grimm[5] later expanded toward the formation of medium-sized rings.

We have been interested in an extension of this reaction where two "equivalent" sulfones are available to react with an ester group. As shown in Scheme 2, we envisioned that

Scheme 2



by strategically placing substituents on the tether joining the two reactive partners, cyclization would preferentially occur to the cyclohexanone containing both substituents in an equatorial disposition. Although addition to the ester is an irreversible process, it is likely that reversible deprotonation

(1) Barluenga, J.; Aznar, F.; Ribas, C.; Valdes, C. *J. Org. Chem.* **1998**, *63*, 10052 and references therein.
(2) Schmalz, H. G.; Schellhaas, K. *Angew Chem., Int. Ed. Engl.* **1996**, *35*, 2146 and references therein.
(3) Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, *8*, 2203 and references therein.
(4) Truce, W. E.; Knospe, R. H. *J. Org. Chem.* **1955**, *77*, 5603.
(5) Grimm, E. L.; Coutu, M. L.; Trimble, L. A. *Tetrahedron Lett.* **1993**, *34*, 7017.

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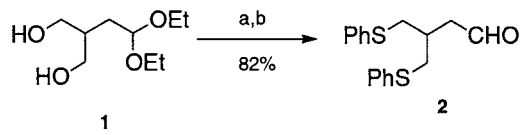
between the sulfonyl groups can occur prior to cyclization. This should favor products with all substituents equatorially positioned on the resulting cyclohexanone.[6]

The products could then serve as extremely valuable synthetic intermediates in organic synthesis since the reactivity of the two resulting sulfone units are remarkably different. For example, selective reduction of the β keto sulfone to the cyclohexanone is a well-known process leaving the remaining sulfone group to then take part in many chemical reactions that it is known to undergo.[7] One could also envision alkylating the keto sulfone before its selective reductive removal, producing a third stereocenter on the cyclohexanone ring.

We began by investigating cyclohexanone precursors and arbitrarily chose to synthesize substrates containing a methyl, isopropyl, and $CH_2OTBDMS$ group at all three positions on the tether. This would deduce whether steric bulk and/or placement (α, β, or γ), relative to the ester moiety, produces the greatest influence on selectivity.

A versatile starting material, which allowed us to access most of the bissulfonyl ester precursors, was the commercially available diol, **1**. After conversion of the diol to the bissulfide[8] followed by hydrolysis of the acetal, we obtained aldehyde **2**, which enabled us to rapidly synthesize most of the cyclization precursors (Scheme 3).

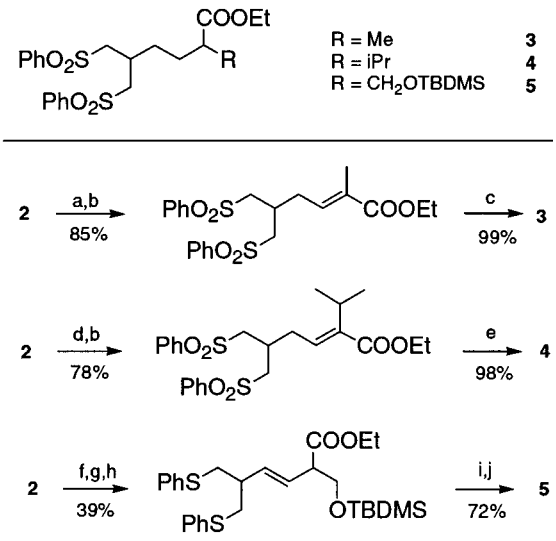
Scheme 3[a]



[a] Key: (a) PBu_3, (phenylthio)phthalimide, THF; (b) HCl(aq), THF.

The syntheses of the α-substituted precursors are shown below in Scheme 4, and all utilize aldehyde **2** as their starting material. All three syntheses involve Horner−Emmons−Wittig reactions to install the ester moiety and either Oxone[9] or hydrogen peroxide[10] protocols to oxidize the sulfides to the corresponding sulfones. Typically hydrogenation sufficed

Scheme 4[a]

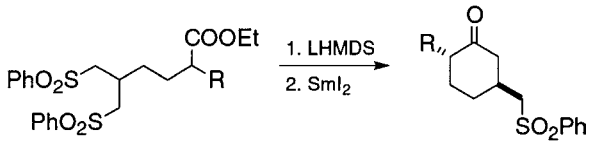


[a] Key: (a) $Ph_3P{=}C(Me)COOEt$, CH_2Cl_2; (b) Oxone, THF/MeOH/H_2O; (c) H_2, Pd/C; (d) $(EtO)_2P(O)CH(^iPr)COOEt$, NaH, THF; (e) $NaBH_4$, $NiCl_2/6H_2O$, EtOH; (f) $Ph_3P{=}CHOOEt$, CH_2Cl_2; (g) LDA, HMPA, CH_2O; (h) TBDMSOTf, NEt_3; (i) Na_2WO_4, H_2O_2, MeOH; (j) H_2, PtO_2, EtOH, 40 psi.

to reduce the olefin but for the isopropyl derivative, **4**, we found that the use of $NaBH_4$ and $NiCl_2$[11] worked best. Introduction of the hydroxy methyl group in **5** was carried out using a deconjugative aldol reaction[12] with formaldehyde followed by reduction of the olefin at a later stage.

Table 1 shows the results upon cyclization[13] followed by

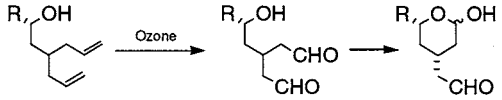
Table 1. Effect of α-Substitution



R	yield (%) (two steps)	dr
Me	66	1.5:1
^{i}Pr	85	3.0:1
$CH_2OTBDMS$	71	3.0:1

Molander[14] reduction of the β-keto sulfone. Yields for the two steps were generally high, and ^1H NMR was used to determine the diastereomeric ratios. Although it appears that larger R groups have some positive affect on the diastereo-

(6) An analogous cyclization was utilized in the synthesis of rhizoxin that involved an in situ preparation of an alcohol with two equivalent aldehydes separated by a three-carbon tether. Presumably through a reversible process, the lactol with all substituents equatorial was formed exclusively. (a) Keck, G. E.; Park, M.; Krishnamurthy, D. *J. Org. Chem.* **1993**, *58*, 3787. (b) Williams, D. R.; Werner, K. M.; Feng, B. *Tetrahedron Lett*, **1997**, *38*, 6825. (c) Burke, S. D.; Hong, J.; Lennox, J. R.; Mongin, A. P. *J. Org. Chem.* **1998**, *63*, 6952.



(7) Simpkins, N. S. In *Sulfones in Organic Synthesis;* Baldwin, J. E., Magnus, P. D., Eds.; Pergamon Press: Oxford, 1993. Oae, S.; Uchida, S. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Striling, C. J. M., Eds.; Wiley: New York, 1988.

(8) Walker, K. A. M. *Tetrahedron Lett.* **1977**, *51*, 4475.

(9) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.

(10) Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963**, *28*, 1140.

(11) See, for example: Hanessian, S.; Grillo, A. T. *J. Org. Chem.* **1998**, *63*, 1049.

(12) Galatsis, P.; Millan, S. D.; Nechala, P.; Ferguson, G. *J. Org. Chem.* **1994**, *59*, 6643.

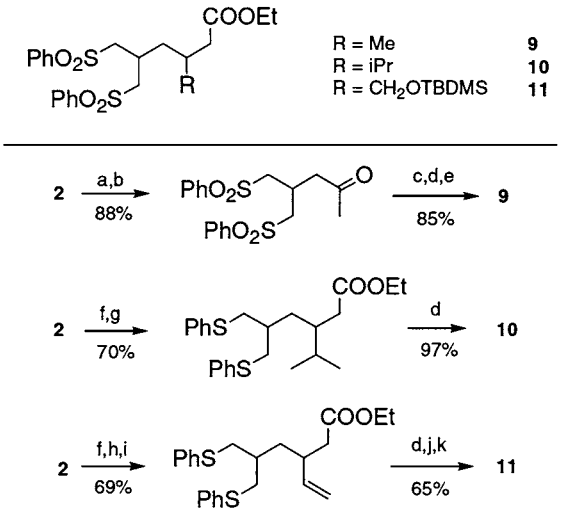
(13) Typically, all precursors were cooled to −78 °C in THF, and 2.2 equiv of LHMDS was added slowly. The solution was stirred for 1 h before the reactions were quenched with saturated NH_4Cl. Yields for the cyclizations were generally very high, and the cyclized adducts were taken to the next step without characterization.

(14) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.

meric ratio, the influence of an α substituent was never larger than 3:1 in favor of the diequatorial product.[15]

The syntheses of the β-substituted precursors are outlined in Scheme 5, and once again, all utilize aldehyde **2** as their

Scheme 5[a]

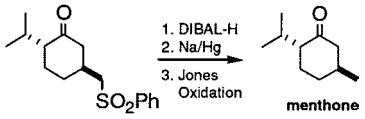


[a] Key: (a) Me_3Al, CH_2Cl_2; (b) Swern oxidation; (c) $(EtO)_2P(O)CH_2COOEt$, NaH; (d) Oxone, THF/MeOH/H_2O; (e) H_2, PtO_2, EtOH; (f) $Ph_3P{=}CHCOOEt$; (g) CuI, TMSCl, ^{i}PrMgCl, tHF, −35 °C; (h) DIBAL-H, PhMe, −50 °C; (i) $CH_3C(OEt)_3$, *o*-nitrophenol, 160 °C; (j) O_3, MeOH/CH_2Cl_2 then $NaBH_4$; (k) TBDMSCl, DMF, imidazole.

starting material. We initially envisioned that a cuprate-based approach would suffice for introduction of the substituents but in practice, only the isopropyl derivative, **10**, could be reproducibly prepared this way in high yield. The methyl substituent was introduced by transforming the aldehyde to a methyl ketone using standard chemistry followed by our previous employed Wittig reaction−hydrogenation sequence to complete the synthesis of **9**. For the CH_2OTBDMS substrate, **11**, we instead found that after reduction of the Wittig product to an allylic alcohol, a Johnson ortho ester rearrangement[16] effectively introduced an ethylene group beta to the ester. Subsequent ozonolysis, reduction, and silylation afforded substrate **11** in good overall yield.

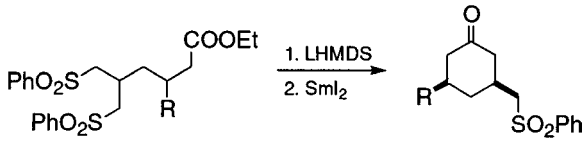
Table 2 shows the results upon cyclization of the β-substituted substrates. Once again, the influence of a β-substituent is not substantial, but it is interesting to note that as the size of the substituent increases the diastereomeric ratio is not affected, unlike the trend seen in Table 1.

(15) Stereochemistry was proven by converting to menthone as shown below and comparison of the ^{13}C NMR of both synthetic and natural products. Similar sequences were carried out for most of the other products as well and are described in the Supporting Information.



(16) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741−743.

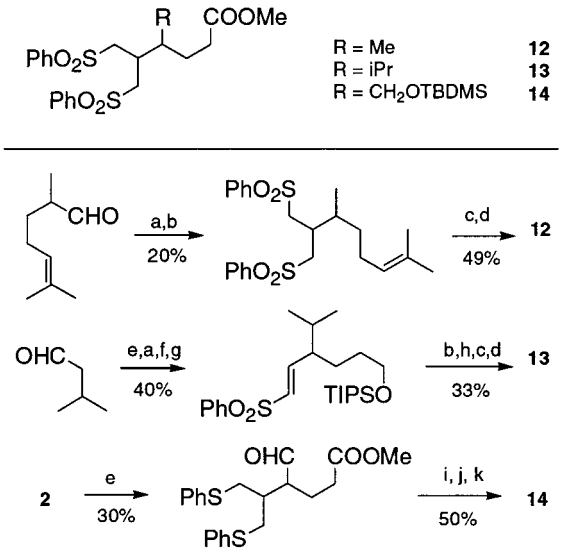
Table 2. Effect of β-Substitution



R	yield (%) (two steps)	dr
Me	62	2.0:1
^{i}Pr	83	2.0:1
CH_2OTBDMS	86	2.0:1

The syntheses of the γ-substituted precursors are outlined in Scheme 6, where it is shown that aldehyde **2** could only

Scheme 6[a]



[a] Key: (a) $(EtO)_2P(O)CH_2SO_2Ph$, LiCl, DBU, CH_3CN; (b) CH_3SO_2Ph, BuLi; (c) $RuCl_3$, $NaIO_4$; (d) CH_2N_2, EtOAc; (d) Oxone, THF/MeOH/H_2O; (e) $TMSNEt_2$, methyl acrylate; (f) DIBAL-H, PhMe; (g) TIPSOTf, Hunig's base, CH_2Cl_2; (h) TBAF, AcOH, THF; (i) MeOH, $NaBH_4$; (j) TBDMSOTf, NEt_3, CH_2Cl_2; (k) Na_2WO_4, MeOH, H_2O_2.

be used for the CH_2OTBDMS precursor, **14**. The carbon skeleton of **14** was constructed using chemistry developed by Hagiwara,[17] which involved a one-pot in situ aldehyde-enamine conversion of aldehyde **2**, followed by Michael addition to methyl acrylate. The aldehyde was then reduced and protected to efficiently produce precursor **14**. The synthesis of substrate **12** began with commercially available 2,6-dimethyl-5-hepten-1-al whereupon a Wittig reaction with Posner's reagent[18] formed the trans unsaturated sulfone in >90% yield. Introduction of the second sulfone unit was accomplished via a Michael addition with the anion of methylphenyl sulfone in an overall yield of 20%.[19] The

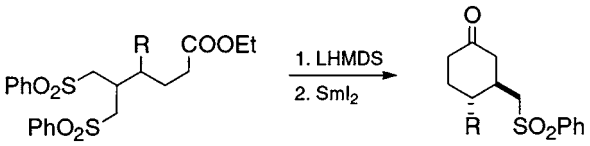
(17) Hagiwara, H.; Komatsubara, H. O.; Okabe, T.; Hoshi, T.; Suzuki, T.; Ando, M.; Kato, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 316.

(18) Posner, G. H.; Brunelle, D. J. *J. Org. Chem.* **1972**, *37*, 3547.

synthesis of **12** was completed by oxidative cleavage[20] of the olefin to the acid and methylation with diazomethane. The synthesis of precursor **13** began with isovaleraldehyde and utilized both the Hagiwara chemistry to introduce the ester group and the Wittig reaction−Michael addition sequence to introduce the bissulfonyl group.

Table 3 shows the results upon cyclization of the γ-substituted substrates. Gratifyingly, it is at this position that substitution produces the greatest effect on the diastereomeric ratio. We also noted that upon increasing the size of the substituent on the tether, the ratio increases from 6:1 up to >20:1. The exact reasons for why γ-substitution gives such an enhancement are not entirely clear yet although experiments are underway to determine whether the deprotonation of the "equivalent" sulfone units is a reversible process prior to cyclization.

Table 3. Effect of γ-Substitution



R	yield (%) (two steps)	dr
Me	53	6.0:1
^{i}Pr	60	>20:1
$CH_2OTBDMS$	76	>20:1

We have introduced a novel cyclization protocol of bissulfone esters that can produce diastereoselectivities as high as 20:1. The best selectivities result when the substituent is placed gamma to the ester moiety. Attempts to increase the diastereomeric ratios regardless of the placement of the substituents are currently underway and involve varying the base, solvent and bulk of the ester moiety. Preliminary results are extremely encouraging, and the full account of these findings will be disclosed soon.

Acknowledgment. We thank Dr. Erich Grimm for his invaluable advice during the course of this project.

Supporting Information Available: Experimental and spectral data (^{1}H NMR, ^{13}C NMR, and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0271436

(19) Although the yield for this transformation is low, it represents the first case to our knowledge of a Michael addition with phenylmethyl sulfone to a vinyl sulfone. We are currently trying to improve the yield for this transformation.

(20) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, B. K. *J. Org. Chem.* **1981**, *46*, 3936.