Enolate Conjugate Addition to Alkylidene Bis-Sulfoxides: Sphaeric Acid Synthesis and Absolute Configuration Determination

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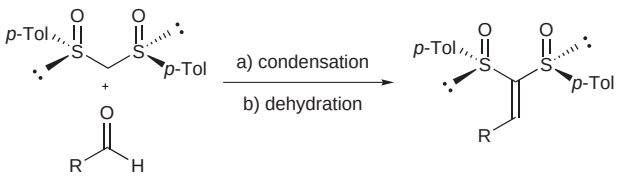
Received 16 December 2005

Abstract: The first stereoselective synthesis of sphaeric acid is described. The key step of this synthesis is an efficient ester enolate conjugate addition onto alkylidene bis-sulfoxides with good to high diastereoselectivity. Formation of sphaeric acid allowed the determination of its absolute configuration as 2*R*,3*R*.

Key words: alkylidene bis-sulfoxides, sphaeric acid, enolate addition, succinic acid, *E*/*Z*-enolate

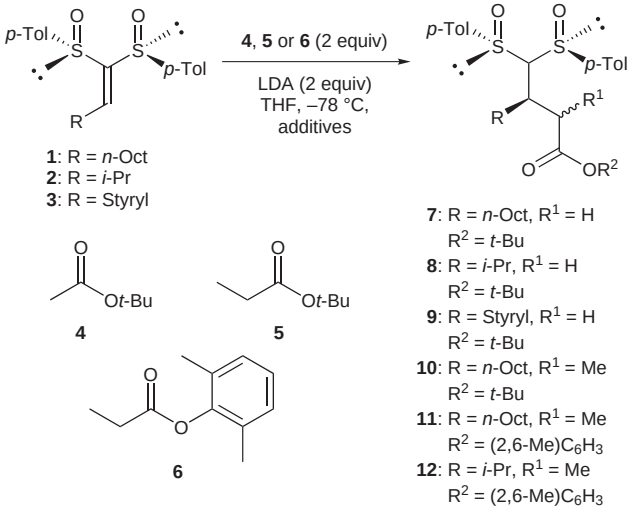
In the field of asymmetric synthesis, alkylidene bis-sulfoxides have been reported as molecules of diverse designs.[1] Their cyclic variants (cyclic dithioacetal dioxides) have been mainly investigated by Aggarwal in cycloaddition reactions or epoxidations.[2] The acyclic variant (bis-*p*-tolylsulfoxides), essentially developed by our group, has shown very attractive features toward asymmetric transformations and more particularly for asymmetric conjugate additions. The use of different nucleophiles, such as amines,[3] alkoxides,[3] organocopper reagents,[3,4] malonate anions,[3,4] and ester enolates, providing enantiopure succinic acid derivatives,[3] has been reported. Recently, the addition of ketone enolates to cyclic alkylidene bis-sulfoxides was reported by Podlech.[5]

Herein, we report new developments in the addition of ester enolates to chiral alkylidene bis-sulfoxide substrates. This transformation will be applied to the total synthesis of succinic acid derivatives, in particular sphaeric acid. The alkylidene (S_S,S_S)-bis(*p*-tolylsulfoxide) derivatives were prepared in good yields according to a previously reported procedure by condensation of the lithium anion of (S_S,S_S)-bis(*p*-tolylsulfoxide)methane with the corresponding aldehyde followed by dehydration of the resulting alcohol (Scheme 1).[6]



Scheme 1

Conjugate addition of ester enolates has been extensively investigated by Heathcock,[7] who has shown the importance of the ester substituents and the enolate configuration on the stereochemical outcome. Esters partners with bulky alcohol substituents (e.g. *tert*-butyl and 2,6-dimethylphenyl) were chosen to avoid Claisen side reactions generating ketoesters and alkoxides. *E*-Enolates were obtained by deprotonation of esters **4**–**6** with LDA in THF at low temperature, while the *Z*-enolates were obtained under the same conditions in the presence of eight equivalents of HMPA.[7d] Enolate addition to the chiral Michael acceptors **1**–**3** proceeded in good to quantitative yield (Scheme 2) affording substituted esters **7**–**12**. The results of conjugate additions are summarized in Table 1.



Scheme 2

The addition of deprotonated *tert*-butyl acetate **4** (R^1 = H) to alkylidene **1** (Table 1, entry 1) afforded the ester **7** in 81% yield with an excellent diasteromeric excess.[8] Only one stereogenic center has been created during this reaction. Thus, like in the case of malonate anion addition,[3] the conjugate addition of an unsubstituted enolate proceeds with complete diastereoselectivity and in high yield. By correlation with previous results[3] we propose absolute *R* configuration for the newly created center.

The same enolate reacted at 0 °C with isopropylidene **2** (Table 1, entry 2) to give **8** quantitatively but the diastereomeric ratio decreased to 88:12. It seems that there is no problem with competitive reactions at higher temperature,

SYNLETT 2006, No. 5, pp 0713–0716
Advanced online publication: 09.03.2006
DOI: 10.1055/s-2006-933122; Art ID: G40005ST

Table 1 Conjugate Addition of the *tert*-Butyl Acetate Enolate of **4**

Entry	Substrate	Products	Yield (%)	dr (**M**/**m**)[a]
1	**1**	**7M**/**7m**	81	>95:5
2	**2**	**8M**/**8m**	quant.	88:12[b]
3	**3**	**9M**/**9m**	88	88:12

[a] **M**: major, **m**: minor.
[b] Reaction carried out at 0 °C.

but a lower temperature is required to ensure high diastereoselectivity. With dienyl bis-sulfoxide **3** (Table 1, entry 3), only 1,4-addition product **9** was detected. The stereochemistry of the carbon β to the ester group was not completely controlled during the addition at –78 °C.

Table 2 Conjugate Addition of the Propionate-Derived Enolate

Entry	Substrate	Ester	Products	Yield (%)	dr (**M**/**m**)[a]
1	**1**	**5**	**10M**/**10m**	80	76:24
2	**1**	**6**	**11M**/**11m**	75	>95:5
3[b]	**1**	**5**	**10M**/**10m**	70	55:45
4[b,c]	**1**	**5**	**10M**/**10m**	81	53:47
5	**2**	**6**	**12M**/**12m**	80	>95:5

[a] **M**: major, **m**: minor.
[b] HMPA (8 equiv).
[c] Reaction carried out at –20 °C.

Under the same conditions, the enolate of *tert*-butyl propionate **5** reacted with octylidene **1** (Table 2, entry 1) to afford the desired product in good chemical yield. Only two (**10M** and **10m**) of the four possible diastereomers were formed. Consistent with the results reported above, the presence of two diastereomers would originate from poor control of the stereogenic center α to the ester.

When the *tert*-butyl group was replaced with the bulkier 2,6-dimethylphenyl group (Table 2, entry 2),[9] the addition of the corresponding enolate (from **6**) to **1** became highly diastereoselective while maintaining a high yield. A single diastereomer **12** was obtained from isopropylidene **2** (Table 2, entry 5). Eight equivalents of HMPA as an additive presumably changed the configuration of the enolate from *E* to *Z*[7d] without modifying the efficiency of the reaction but decreased the diastereoselectivity dramatically (Table 2, entries 3 and 4). This diastereoselectivity was also affected by a higher temperature (Table 2, entry 4). Importantly, the same two diastereomers **10M** and **10m** were obtained with and without HMPA.

We propose a diastereoselectivity model in order to rationalize the different results reported above. This model (Figure 1) involves steric interactions between alkylidene and enolates according to their conformation and configuration.

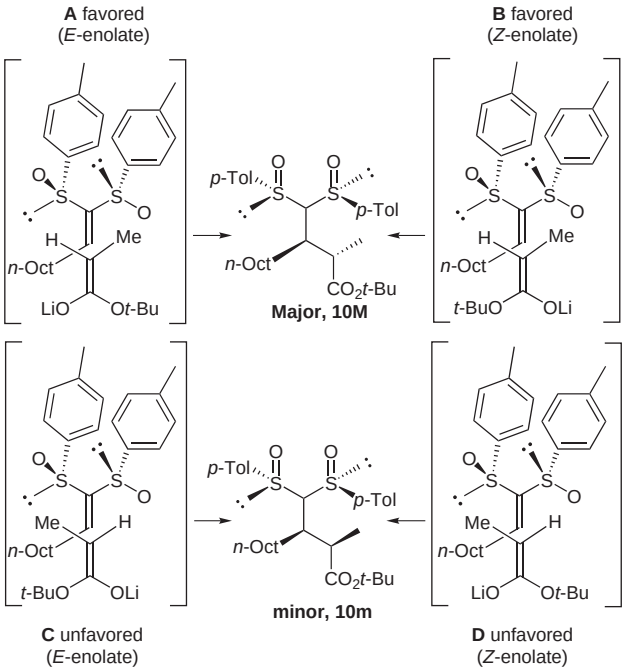
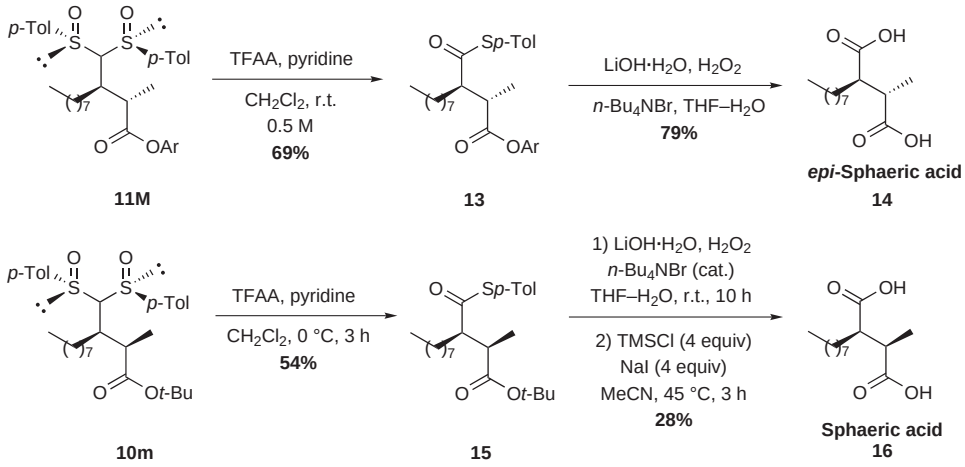


Figure 1

The alkylidene bis-sulfoxide adopts a conformation where the lone pair of one sulfinyl group is quasi-eclipsing the *syn* R^1 group on the alkene, the second sulfinyl group is in an s-*cis* position, and the two tolyl groups are face-to-face stabilized by a π-stacking interaction.[3] The attack on the *re* face of the alkylidene is blocked by the two aromatic rings while the nucleophile approaches the *si* face, maintaining the Bürgi–Dunitz angle.[10] Two transition states are proposed for the *E*-enolate (**A** and **C**) and two for the *Z*-enolate (**B** and **D**). For each enolate configuration, the favored transition state (**A** or **B**) avoids the steric interaction between the methyl and the alkyl chain. A synergic effect from the steric interaction from the R^2 group would take place and a high diastereoselectivity is obtained with a 2,6-dimethylphenyl group. In this case, destabilization of the transition state originating from **C** is increased and the amount of the minor diastereomer formed is reduced. The lack of diastereoselectivity with the *Z*-enolate could be explained by the dissociative effect of HMPA on the lithium enolate aggregates. The OLi unit becomes less sterically demanding and the differentiation between OLi and OR^2 is weaker than without HMPA. Thus, transition states **B** and **D** would be energetically close and the proportion of minor diastereomer increases.

We targeted succinic acid derivatives and more specifically sphaeric and *epi*-sphaeric acid. Sphaeric acid was isolated in 1999 by Strobel from the fermentation broth of *Sphaeropsis sp.*[11] This succinic acid derivative has exhibited two interesting biological activities. The first is a selective antibiotic activity against *Staphylococcus aurus* and *Bacillus subtilis*. This compound also exhibits interaction with interleukin-1 that plays an important role in the immune system. Six years after its first isolation, only the relative configuration of sphaeric acid is known.



Scheme 3

Sphaeric and *epi*-sphaeric acids were synthesized enantiomerically pure (Scheme 3). Compound **11M** (Table 2, entry 2) underwent a Pummerer reaction with trifluoacetic anhydride in the presence of pyridine; thioester **13** was isolated in 69% yield. Saponification of the two esters groups by lithium hydroxide/hydrogen peroxide in THF–water with a phase transfer catalyst allows the formation of *epi*-sphaeric acid **14** in 79% yield.[12] The absolute configuration of **14** was determined by correlation with the NMR data of roccellic acid, with which it showed very high spectral similarity.[3]

The diastereomer **10m** (Table 2, entry 4) was treated with trifluoroacetic anhydride and pyridine in dichloromethane at 0 °C to yield the thioester **15** in 54% yield as a single diastereomer. In this case, two different saponification reactions were necessary to obtain sphaeric acid **16**. Lithium hydroxide/hydrogen peroxide allowed the cleavage of the thioester group generating the first carboxylic acid while the *tert*-butyl ester is not hydrolyzed. Chlorotrimethylsilane and sodium iodide are used to saponify this unreactive ester.[13] Sphaeric acid **16** was isolated in 28% yield for the last two steps.[14] All the spectroscopic and analytical data are similar to the reported characterization of sphaeric acid **16** {$[\alpha]_D^{20}$ +8.1 (*c* 0.78, MeOH), Lit. $[\alpha]_D^{20}$ +7.0 (*c* 0.90, MeOH)}.[11] Thus, we determined the absolute configuration of sphaeric acid as 2*R*,3*R* and we confirmed the relative stereochemistry proposed by Strobel.

In conclusion, we reported an efficient and diasteroselective conjugate addition of *E*- and Z-enolates to different acyclic alkylidene bis-sulfoxides. Complete diastereoselectivity is observed with the 2,6-dimethylphenyl group on the ester residue. The first asymmetric total synthesis of biologically active sphaeric acid has been developed by this methodology and the absolute configuration of this succinic acid derivative has been determined.

Acknowledgment

The authors thank the Ministère de l'Education Nationale for a PhD grant to F.B. M.M. is a member of Institut Universitaire de France and we thank IUF for financial support. We thank Gary Strobel for providing the NMR spectra of the original sample of sphaeric acid.

References and Notes

(1) (a) The more accurate name is 'alkenylidene bis-sulfoxides' but 'alkylidene bis-sulfoxides' is conveniently used in analogy with the corresponding malonate derivatives. (b) For a review on bis-sulfoxides, see: Delouvrié, B.; Fensterbank, L.; Nájera, F.; Malacria, M. *Eur. J. Org. Chem.* **2002**, 3507.

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(8) **Enolate Conjugate Addition**
General Procedure A (*E*-Enolate): To a solution of LDA (2 equiv) in THF (2.4 mL/mmol) at –78 °C, a solution of ester (2 equiv) in THF (1.4 mL/mmol) was added. After 45 min at –78 °C, a solution of alkylidene bis-sulfoxide (1 equiv) in THF (4.8 mL) was added via cannula. The reaction mixture was stirred at –78 °C for 15 min, quenched with an aq sat. solution of NH_4Cl, and diluted with CH_2Cl_2. The organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography.

Procedure B (*Z*-Enolate): To a solution of LDA (2 equiv) in THF (2.4 mL/mmol) at –78 °C, freshly distilled HMPA (8 equiv) and a solution of ester (2 equiv) in THF (1.4 mL/mmol) was added. After 45 min at –78 °C, a solution of alkylidene bis-sulfoxide (1 equiv) in THF (4.8 mL) was added via cannula. The reaction mixture was stirred at –78 °C for 15 min, quenched with an aq sat. solution of NH_4Cl and diluted with CH_2Cl_2.The organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography.

(*S*$_S$,*S*$_S$,3*R*)-3-[Bis(*p*-tolylsulfinyl)methyl]undecanoic Acid *tert*-Butyl Ester (7): Prepared by general procedure A from **1** (50 mg, 0.12 mmol). Column chromatography (pentane–EtOAc, 90:10 to 80:20) afforded 52 mg (81%) of **6** as a colorless oil; $[\alpha]_D^{20}$ +79.0 (*c* 0.4, $CHCl_3$). IR (neat): 2926, 2855, 1728, 1492, 1367, 1152, 1086, 1058, 811, 755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 0.90–1.27 (m, 14 H, 7 × CH_2), 1.42 [s, 9 H, $C(CH_3)_3$], 2.31 (s, 3 H, *p*-Tol), 2.44 (s, 3 H, *p*-Tol), 2.69 [dd, *J* = 16.6, 8.6 Hz, 1 H, C*H*H$CO_2C(CH_3)_3$], 2.82 [m, 1 H, C*H*CH(SO*p*-Tol)$_2$], 3.18 [dd, *J* = 16.6, 3.3 Hz, 1 H, CH*H*$CO_2C(CH_3)_3$], 3.60 [d, *J* = 4.4 Hz, 1 H, C*H*(SO*p*-Tol)$_2$], 6.88 (d, *J* = 8.2 Hz, 2 H, Ar), 7.12 (d, *J* = 8.0 Hz, 2 H, Ar), 7.37 (d, *J* = 8.0 Hz, 2 H, Ar), 7.54 (d, *J* = 8.2 Hz, 2 H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4 (CH_2CH_3), 21.5 (*p*-Tol), 21.8 (*p*-Tol), 22.9, 26.7, 29.2, 29.3, 29.6, 32.1, 32.6 (7 × CH_2), 28.4 [C(*C*H$_3$)$_3$], 31.5 [*C*HCH(SO*p*-Tol)$_2$], 37.3 [*C*H$_2$CO$_2$C(CH$_3$)$_3$], 80.8 [CO$_2$*C*(CH$_3$)$_3$], 89.2 [*C*H(SO*p*-Tol)$_2$], 124.0 (2 C, ArCH), 125.0 (2 C, ArCH), 130.1 (2 C, ArCH), 130.4 (2 C, ArCH), 139.2, 140.9, 141.2, 142.3 (4 C, ArCH), 171.8 (CO). HRMS: *m*/*z* calcd for $C_{30}H_{44}O_4NaS_2$ [M + Na]$^+$: 555.2579; found: 555.2584.

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(12) ***epi*-Sphaeric Acid (14)**: White solid; mp 121–125 °C (dec.); $[\alpha]_D^{20}$ +18.9 (*c* 1.1, CH_3OH). IR (neat): 3100, 2918, 2852, 2615, 1689, 1462, 1419, 1275, 1198, 945 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 0.93 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.19 (d, *J* = 6.6 Hz, 3 H, CH_3CH), 1.32 (br s, 12 H, 6 × CH_2), 1.51 (m, 1 H, CH_2), 1.63 (m, 1 H, CH_2), 2.54–2.62 (m, 2 H, 2 × *C*HCOOH). ^{13}C NMR (100 MHz, CD_3OD): δ = 15.3 (CH_3), 16.9 (CH_3CH), 24.6, 29.3, 31.2, 31.3 (2 C), 32.9, 33.9 (7 × CH_2), 44.4, 51.0 (2 × *C*HCOOH), 178.9, 179.5 (2 × COOH). HRMS: *m*/*z* calcd for $C_{13}H_{24}NaO_4$ [M + Na]$^+$: 267.1572; found: 267.1602.

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(14) **Sphaeric Acid (16)**: Colorless oil; $[\alpha]_D^{20}$ +8.1 (*c* 0.78, MeOH). IR (neat): 3027, 3018, 2924, 2855, 2680, 1705, 1464, 1416, 1282, 1240, 932 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.6 Hz, 3 H, CH_2CH_3), 1.27–1.36 (m, 15 H, 6 × CH_2, CH_2CH_3), 1.56–1.63 (m, 2 H, CH_2), 2.57 (dt, 1 H, *J* = 9.6, 4.3 Hz, CH), 2.72 (dq, *J* = 9.8, 4.2 Hz, 1 H, CH), 11.04 (br s, 2 H, CO_2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 15.2 (CH_3), 22.7, 26.5, 29.2 (2 C), 29.3, 29.5, 31.8 (7 × CH_2), 40.9, 47.9 (2 *C*HCOOH), 181.9, 182.5 (2 × COOH).