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Asymmetric Diels−Alder Reactions of a New Enantiomerically Pure Sulfinylquinone: A Straightforward Access to Functionalized Wieland−Miescher Ketone Analogues with (*R*) Absolute Configuration

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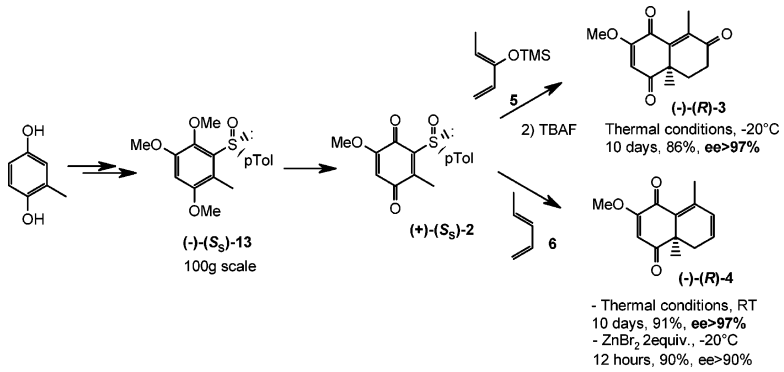

An efficient and highly stereocontrolled preparation, on a large scale, of two new Wieland−Miescher-type diketones is described. The approach centers on a diastereoselective Diels−Alder reaction using a new enantiomerically pure sulfinylquinone. Mechanistic investigations of this cycloaddition on several dienes are described.

Introduction

Since the pioneering works of Hajos[1] and Eder,[2] optically active Wieland−Miescher-type diketones **1** (Figure 1) have been employed as key starting materials for the total synthesis of various natural products including terpenoids and steroids.[3,4] Recently, the first total synthesis of the neoclerodane (−)-methyl barbascoate from diketone (−)-(*R*)-**1** (R = Me) was reported (Figure 1).[3a] The availability in large scale of more functionalized Wieland−Miescher-type diketones such as **3** (Figure 2) should open synthetic routes to more complex neoclerodanes with attractive pharmacological properties (e.g., salvinorins[5a] or salvinicins[5b]).

We recently initiated a program directed toward terpenoid synthesis using diastereoselective Diels−Alder reactions of the enantiomerically pure (S_S)-5-methoxy-2-methyl-3-(*p*-tolylsulfinyl)-1,4-benzoquinone **2** (Scheme 1) to construct a functionalized skeleton with an angular methyl group.

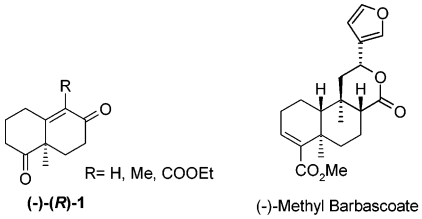

FIGURE 1. Wieland-Miescher-type diketones **1** and structure of (−)-methylbarbascoate.

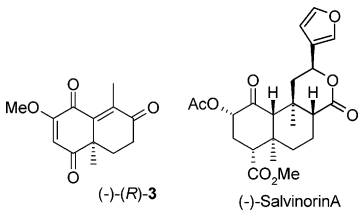

FIGURE 2. Wieland-Miescher-type triketone **3** and structure of salvinorin A.

(1) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

(2) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496.

(3) See, for exemple: (a) Hagiwara, H.; Hamano, K.; Hoshi, T.; Suzuki, T.; Kido, F. *J. Org. Chem.* **2005** *70*, 2250. (b) Ling, T.; Chowdhury, C.; Kramer, B. A.; Vong, B. C.; Palladino, M. A.; Theodorakis, E. A. *J. Org. Chem.* **2001**, *66*, 8843. (c) Katoh, T.; Nakatani, M.; Shikita, S.; Sampe, R.; Ishiwata, A.; Ohmori, O.; Nakamura, M.; Terashima, S. *Org. Lett.* **2001**, *3*, 2701. (d) Banerjee, A. K.; Laya-Mimo, M. *Stud. Nat. Prod.* **2000**, 175.

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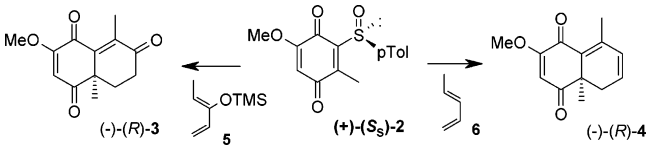
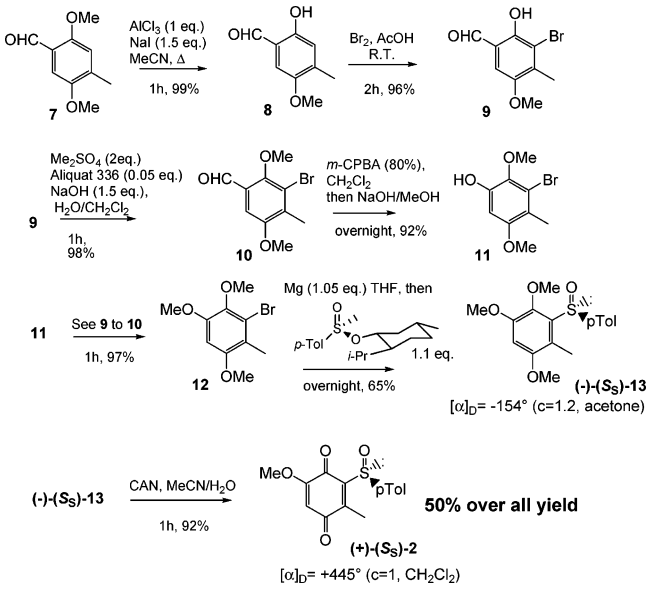
SCHEME 1



The use of sulfinyl benzoquinones as dienophiles for Diels−Alder reactions has experienced increased interest in recent years.[6,7] This methodology found its first synthetic application in the enantioselective synthesis of angucyclinones using an enantiomerically pure sulfinyl naphthaquinone as dienophile.[8] Further investigations allowed the construction of enantiomerically pure angucyclinone-type skeletons via a tandem cycloaddition/pyrolytic sulfoxide elimination sequence with kinetic resolution of the racemic semicyclic dienes.[9]

The presence of a substituent in the starting quinone generally influences the chemoselectivity of the cycloaddition. For example, cycloaddition of (S_S)-2-substituted 3-*p*-tolylsulfinyl-1,4-benzoquinones with acyclic and cyclic dienes takes place preferentially on the unsubstituted dienophilic double bond.[10] In light of the preceding work[6,7,9] on sulfinylquinone cycloadditions, we reasoned that the presence of a methoxy group at the C-5 position should modify the behavior of the new dienophile and that the sulfinyl group should control the stereochemical course of the cycloaddition.

SCHEME 2. Synthesis of (+)-(S_S)-5-Methoxy-2-methyl-3-(*p*-tolylsulfinyl)-1,4-benzoquinone 2



Here, we report an efficient synthesis[11] on a multigram scale of the previously unknown (S_S)-5-methoxy-2-methyl-3-(*p*-tolylsulfinyl)-1,4-benzoquinone **2** and a straightforward access to highly functionalized and enantiomerically pure Wieland−Miescher-type triketone **(−)-(*R*)-3** and diketone **(−)-(*R*)-4** via a Diels−Alder reaction between **2** and dienes **5** and **6** (Scheme 1).

Results and Discussion

(+)-(S_S)-Sulfinyl benzoquinone **2** was synthesized by using aldehyde **7**, which was easily prepared in two steps[12] from inexpensive 2-methylhydroquinone, according to the sequence given in Scheme 2.

Initial attempts to introduce bromine directly on aldehyde **7** led to a mixture of regioisomers. The transformation was carried out successfully by releasing the ortho-directing phenol group. Selective demethylation of **7** using regioselective conditions ($AlCl_3$/NaI, reflux in MeCN) proceeded smoothly to give phenol **8** in quantitative yield. Ortho-bromination followed by protection of the free alcohol afforded the bromide **10** in 94% yield for two steps. A Baeyer−Villiger/hydrolysis process followed by protection of the resulting phenol group provided the bromide **12** in high yield. It should be observed that this precursor **12** could be prepared easily within one week from aldehyde **7** in batches larger than 100 g using only crystallizations for purifications. Furthermore, the use of crude products from **7** to **12** is possible, but in this case a chromatography of the final bromide **12** is necessary.

(4) Tokoroyama, T. *Synthesis* **2000**, *5*, 611. Advanced precursors of natural products: (a) Kawano, H.; Itoh, M.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1997**, *38*, 7769. (b) Kawai, N.; Takao, K.-I.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 4193. (c) Nakatani, M.; Nakamura, M.; Suzuki, A.; Inoue, M.; Katoh, T. *Org. Lett.* **2002**, *4*, 4483. (d) Coltart, D. M.; Danishefsky, S. J. *Org. Lett.* **2003**, *5*, 1289. (e) Ling, T.; Rivas, F.; Theodorakis, E. A. *Tetrahedron Lett.* **2002**, *43*, 9019. (f) Markó, I. E.; Wiaux, M.; Warriner, S. M.; Giles, P. R.; Eustace, P.; Dean, D. Bailey, M. *Tetrahedron Lett.* **1999**, *40*, 5629. (g) Takao, K.-I.; Kobayashi, S. *Tetrahedron Lett.* **1997**, *38*, 6685. Total synthesis of (+)-atisirene: (h) Ihara, M.; Toyota, M.; Fukumoto, K. Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2151. Total synthesis of antibacterial clerodane: (i) Hagiwara, H.; Inome, K.; Uda, H. *Tetrahedron Lett.* **1994**, *35*, 8189. Total synthesis of (+)-dysideapalaunic acid: (j) Hagiwara, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1803. Total synthesis of (−)-ilimaquinone: (k) Bruner, S. D.; Radeke, H. S.; Tallarico, J. A.; Snapper, M. L. *J. Org. Chem.* **1995**, *60*, 1114. Total synthesis of (+)-avarol and (+)-avarone: (l) An, J.; Wiemer, D. F. *J. Org. Chem.* **1996**, *61*, 8775.(m) Ling, T.; Xiang, A. X.; Theodorakis, E. *Angew. Chem., Int. Ed.* **1999**, *38*, 3089. Total synthesis of (−)-ilimaquinone analogues: (n) Radeke, H. S.; Digits, C. A.; Bruner, S. D.; Snapper, M. L. *J. Org. Chem.* **1997**, *62*, 2823. Total synthesis of (−)-dysidiolide: (o) Corey, E. J.; Roberts, B. E. *J. Am. Chem. Soc.* **1997**, *119*, 12425. Sesquiterpenes: (p) Poigny, S.; Guyot, M.; Samadi, M. *J. Org. Chem.* **1998**, *63*, 5890. Total synthesis of nakijiquinones: (q) Stahl, P.; Waldmann, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 3710. Total synthesis of (+)-aureol: (r) Suzuki, A.; Nakatani, M.; Nakamura, M.; Kawaguchi, K.; Inoue, M.; Katoh, T. *Synlett* **2003**, 329

(5) (a) Salvinorins A and B: Ortega, A.; Blount, J. F.; Manchand, P. S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2505. Valdés, L. J., III; Butler, W. M.; Hatfield, G. M.; Paul, A. G.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 4716. Salvinorin C: Valdés, L. J., III; Chang, H.-M.; Visger, D. C.; Koreeda, M. *Org. Lett.* **2001**, *3*, 3935. Salvinorins D−F: Munro, T. A.; Rizzacasa, M. A. *J. Nat. Prod.* **2003**, *66*, 703. (b) Harding, W. W.; Tidgewell, K.; Schmidt, M.; Shah, K.; Dersch, C. M.; Snyder, J.; Parrish, D.; Deschamps, J. R.; Rothman, R. B.; Prisinzano, T. E. *Org. Lett.* **2005**, *7*, 3017.

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(7) Hanquet, G.; Colobert, F.; Lanners, S.; Solladié, G. *ARKIVOC* **2003**, *(vii)*, 328.

(8) Carreño, M. C.; Urbano, A.; Fischer, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1621.

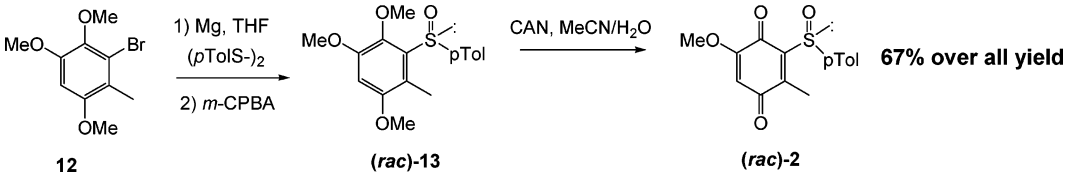
(9) (a) Carreño, M. C.; Urbano, A.; Di vitta, C. *J. Org. Chem.* **1998**, *63*, 3, 8320; *Chem. Eur. J.* **2000**, *6*, 906. (b) For racemic sulfinylquinone resolution using enantiopure semicyclic dienes, see: Carreño, M. C.; Urbano, A.; Ribagorda, M.; Somoza, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2755.

(10) Carreño, M. C.; Garcia Ruano, J. L.; Toledo, M. A.; Urbano, A. *Tetrahedron Lett.* **1994**, *35*, 9759.

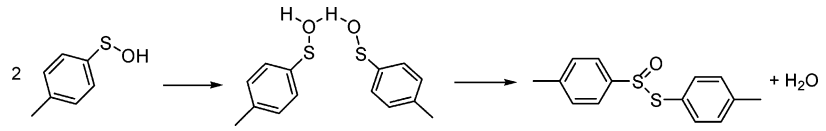
(11) For the difference between an "efficient" and an "effective" synthesis see: Heathcock, C. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 665.

(12) Standridge, R. T.; Howell, H. G.; Gylys, J. A.; Partyka, R. A.; Shulgin, A. T. *J. Med. Chem.* **1976**, *19*, 1400.

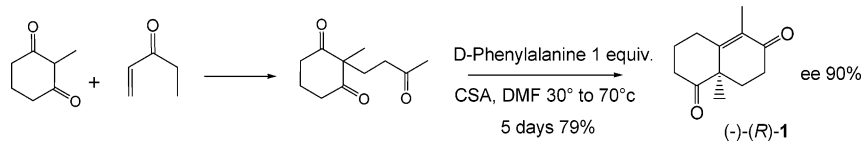
SCHEME 3. Synthesis of *rac*-5-Methoxy-2-methyl-3-(*p*-tolylsulfinyl)-1,4-benzoquinone 2



SCHEME 4. Self-Condensation of *p*-Tolylsulfenic Acid to *p*-Tolyl Disulfide Oxide



SCHEME 5. Hagiwara's Procedure to Diketone (−)-(*R*)-1

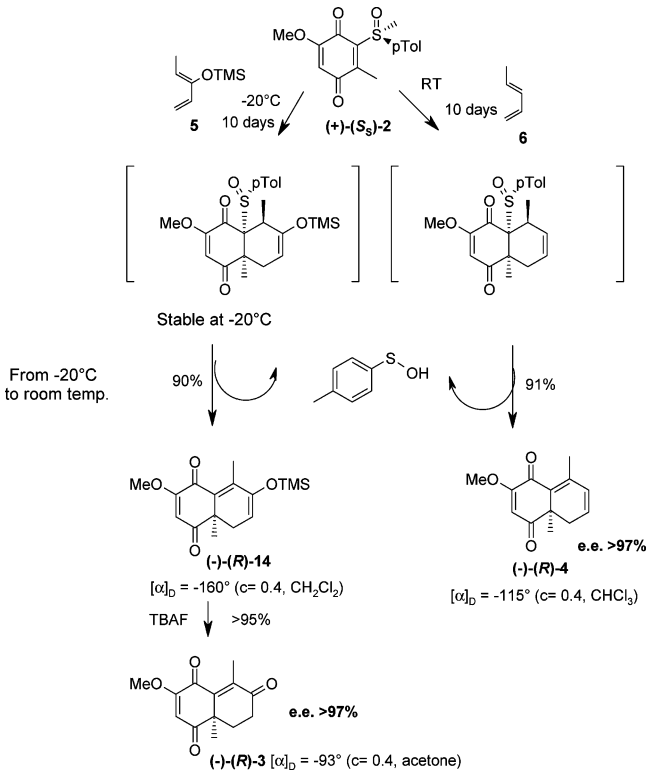


Metalation and sulfinylation[13] of **12** with (−)-(S_S)-menthyl-*p*-toluenesulfinate afforded sulfoxide **13** in 65% yield after trituration in diethyl ether. Finally, direct oxidative demethylation using cerium ammonium nitrate (CAN) afforded the desired (S_S)-5-methoxy-2-methyl-3-(*p*-tolylsulfinyl)-1,4-benzoquinone **2** in high yield as orange needles after crystallization in methanol. The enantiomeric purity (>98%) of the sulfinyl quinone **2** has been measured by ^{1}H NMR spectroscopy using Eu(tfc)$_3$ as a chiral lanthanide shift reagent. The racemic compound (±)-**2**, necessary for such a determination, was synthesized from **12** in three steps (Scheme 3).

We next investigated the reactivity of the enantiomerically pure dienophile **2** toward the diene **5** obtained from ethylvinyl ketone,[14] or piperylene **6** in order to prepare functionalized Wieland−Miescher-type triketone **3** and diketone **4**. Our goal was to use the simplest chemistry applicable in large scale providing large quantities of chiral starting material for total synthesis of complex neoclerodanes. The best results were achieved working in CH_2Cl_2 at −20 °C for **5** and at room temperature for **6**. Under these conditions, Diels−Alder reaction between quinone (+)-**2** and 2 equiv of dienes **5** and **6** gave rise within 10 days respectively to mixtures of cycloadduct **14** or **4** (ee >97%) and *p*-tolyl disulfide oxide resulting from the spontaneous pyrolytic elimination of the sulfinyl group of the initially formed cycloadduct in the reaction mixture (Scheme 6). This elimination produced sulfenic acid which self-condensed to *p*-tolyl disulfide oxide quite slowly at room temperature (Scheme 4).[15]

The *p*-tolyl disulfide oxide is recovered after chromatography of the crude mixture. Despite the quite long reaction time required to obtain a total conversion, we point out that the preparation of the less functionalized Wieland−Miescher diketone (−)-(*R*)-**1** from 2-methyl-1,3-cyclohexanedione using optimized Hagiwara's protocol requires 5 days (for the annelation step) and also stoechiometric amounts of chiral catalyst (Scheme 5).[16]

SCHEME 6. Cycloaddition of Sulfinylquinone 2 with Dienes 5 and 6



Chromatography of the reaction mixture on demetalated silica gel[17] delivered cycloadducts **14** and **4** in 90% yield. Subsequent

(13) (a) Andersen, K. K.; Gaffield, W.; Papanikolaou, N. E. *J. Am. Chem. Soc.* **1964**, *56*, 5635. (b) Carreño, M. C.; Garcia Ruano, J. L.; Urbano, A. *Synthesis* **1992**, 651. (c) Girardin, A.; Hutt, J.; Solladié, G. *Synthesis* **1987**, 173. (d) Hajipour, A. R.; Falahati, A. R.; Ruoho, E. *Tetrahedron Lett.* **2006**, *47*, 2717.

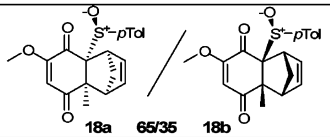
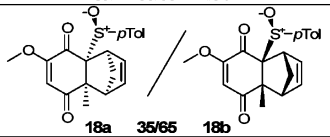
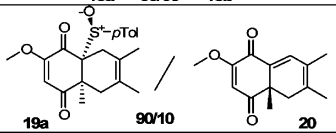
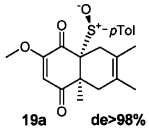
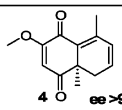
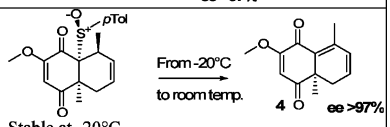
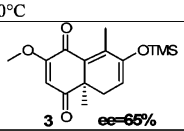
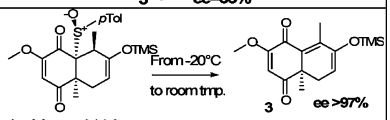
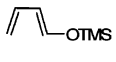
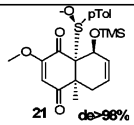
(14) Belanger, J.; Landry, N. L.; Pare, J. R.; Jankowski, K *J. Org. Chem.* **1982**, *47*, 3649.

(15) (a) Barrett, G. C. In *The chemistry of sulphenic acids and their derivatives*; Pataï S, Ed.; John Wiley and Sons: Chichester, 1990; p 1. (b) Hogg, D. R. In *The chemistry of sulphenic acids and their derivatives*; Pataï S, Ed.; John Wiley and Sons: Chichester, 1990; p 361. (c) Davies, F. A.; Jenkins, L. A.; Billmeis, R. L. *J. Org. Chem.* **1986**, *51*, 1033.

(16) Hagiwara, H.; Uda, H. *J. Org. Chem.* **1988**, *53*, 2308.

(17) Chromatography of reaction mixtures using standard silica gel afforded (*R*)-**4** in 75% yield and a mixture of (*R*)-**3** and (*R*)-**14** in only 15 and 20% yield, respectively. For demetalated silica gel preparation, see: Hubbard, J. S.; Harris, T. M. *J. Org. Chem.* **1981**, *46*, 2566.

TABLE 1. Cycloaddition of Sulfinylquinone 2 with Dienes 5, 6, and 15−17 in CH_2Cl_2

Entry	Diene	Time[c]	Temp.	Isolated Yields	Products
1	 15	4 days	20°C	78%[a]	 18a 65/35 18b
2		12 days	-20°C	80%[a]	 18a 35/65 18b
3	 16	12 days	20°C	81%[b]	 19a 90/10 20
4	 16	45 days	-20°C	85%	 19a de>98%
5	 6	10 days	20°C	90%	 4 ee >97%
6	 6	45 days	-20°C	90%	 Stable at -20°C From -20°C to room temp. 4 ee >97%
7	 5	30 hours	20°C	88%	 3 ee=65%
8	 5	10 days	-20°C	91%	 Stable at -20°C From -20°C to room tmp. 3 ee >97%
9	 17	10 hours	20°C	96%	 21 de>98%

[a] Isolated yields of diastereoisomers **18a** and **18b** mixture. [b] Sulfenic acid elimination from minor diastereoisomer **19b** occurred in the reaction mixture. [c] Time for total disappearance of sulfinylquinone **2** on ^{1}H NMR spectra of the crude mixture.

treatment of compound **14** with TBAF led in high yield to triketone **3** which can be crystallized in ether. The enantiomeric excess (>97%) of triketone **3** and diketone **4** were determined by ^{1}H NMR spectroscopy using $Eu(tfc)_3$ as a chiral lanthanide shift reagent.[18]

As expected, the presence of a methoxy group at the C-5 position led to an exclusive reaction through C-2-C-3 sulfinyl substituted double bond in these reactions, and the very high π-facial diastereoselectivities observed agrees with previous results reported in the literature.[20,7] To rationalize the stereochemical outcome of this reaction, we chose three other dienes **15**−**17** and compared their reactivity toward the sulfinyl-quinone **(**S_S**)-2** in CH_2Cl_2 at room temperature or −20 °C with dienes **5** and **6** (Table 1).

For all dienes we observed that cycloadditions performed at −20 °C led to stable adducts bearing the sulfinyl moiety. The pyrolysis process depended on the structure of the cycloadducts and occurred only at room temperature (entries 6 and 8).

Under these conditions, Diels−Alder reactions between quinone (S_S)-**2** and 2 equiv of dienes **16** and **17** gave rise to the optically active cycloadducts **19a** and **21** as major or exclusive diastereoisomer in excellent yields (entries 3, 4, and 9). No spontaneous sulfoxide moiety elimination was observed at room temperature for the major diastereoisomer **19a**, and attempts to initiate the sulfenic acid elimination under various conditions (refluxing in toluene, heating in basic or acidic medium) were ineffective. In sharp contrast, this elimination occurred spontaneously with the minor diastereoisomer **19b** in the reaction

(18) Racemic triketone (±)-**3** and diketone (±)-**4** were prepared from racemic sulfinyl benzoquinone **2**.

(19) VCD/IR measurements and analysis were performed by Prof. T. Freedman.

(20) Freedman, T. D.; Nafie, L. A.; Cao, X. Dukor, K. *Chirality* **2003**, *15*, 734.

(21) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717.

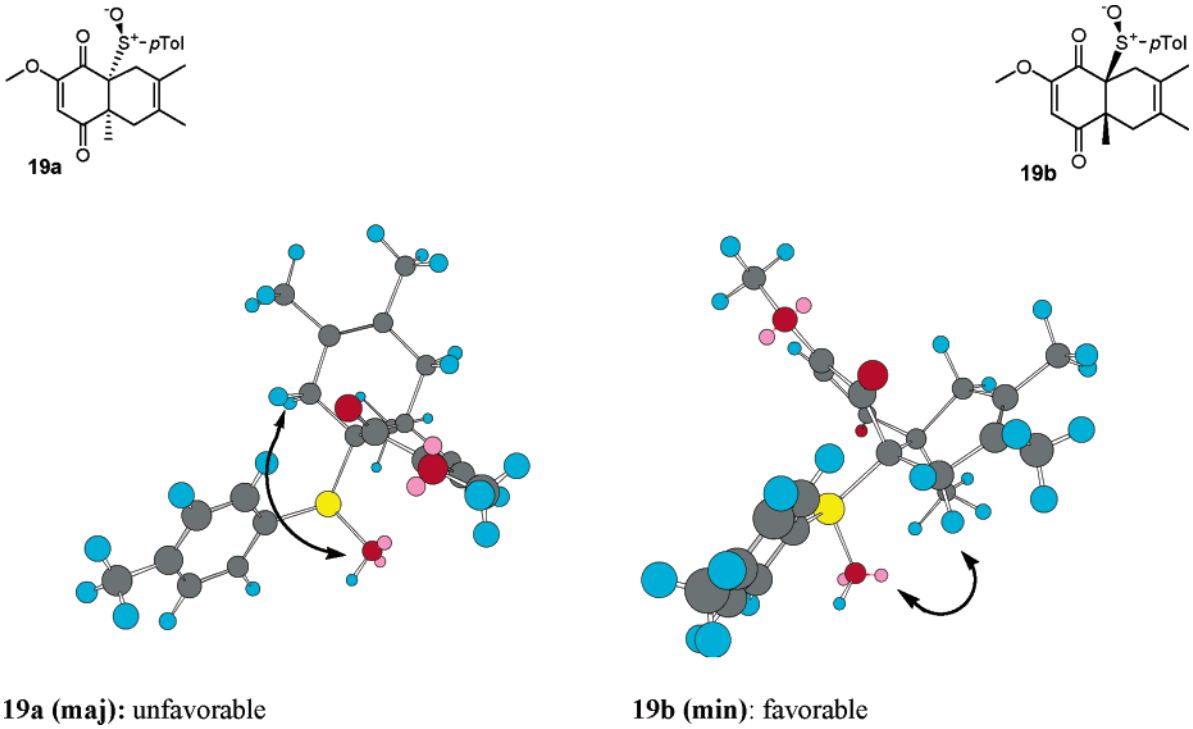


FIGURE 3. Qualitative energy minimization (MM2) of **19a** and **19b**.

mixture at room temperature (entry 4). The corresponding adduct **20** resulting from the cycloaddition/sulfenic acid elimination process was recovered in 7% yield after chromatography. We suppose that in the case of cycloadduct **19a**, none of the hydrogen atoms α to the sulfinyl group were in a favorable conformation to allow a *syn*-elimination (Figure 3).

The results collected in Table 1 showed that the stereochemical course of the reaction was correlated with temperature for acyclic dienes. Decrease of the temperature increased reaction time and increased diastereoselectivity. For example, the reactions of dienes **5** and **16** were moderately selective at 20 °C (entries 3 and 7) and became totally diastereoselective at −20 °C to deliver compounds **3** (after sulfenic acid elimination at room temperature) and **19a** as single products (entries 3 and 7). Totally diastereoselective cycloaddition with quinone (S_S)-**2** occurred with dienes **6** and **17** even at 20 °C (entries 5 and 9).

The C-5 methoxy-induced chemoselectivity toward the C_2-C_3 double bond was clearly illustrated when the cycloaddition was performed with cyclopentadiene. Carreño described few years ago[6a] a chemoselective cycloaddition of (S_S)-2-*p*-tolylsulfinyl-1,4-benzoquinone with cyclopentadiene exclusively on C_5-C_6 double bond. In our case, despite the presence of an unfavorable methyl substituant at the C-2 position, no cycloadduct resulting from C_5-C_6 double bond reaction was observed. Only clean mixture of **18a** and **18b** was formed. The diastereoisomeric ratio **18a**/**18b** was determined directly from the crude reaction mixture by ^{1}H NMR analysis, and **18a**/**18b** were readily separated by flash chromatography. Unexpectedly, this ratio was inverted at −20 °C (entry 2).

In sharp contrast with cyclopentadiene, acyclic dienes **5**, **6,** and **16** afforded highly diastereoselective cycloadditions at −20 °C, leading exclusively to adducts bearing the sulfinyl moiety. A rapid work up of the reaction mixtures gave these cycloadducts as solids stable upon storage at −20 °C. The sulfinyl *syn*-elimination occurred for the adducts proceeding from dienes **5**

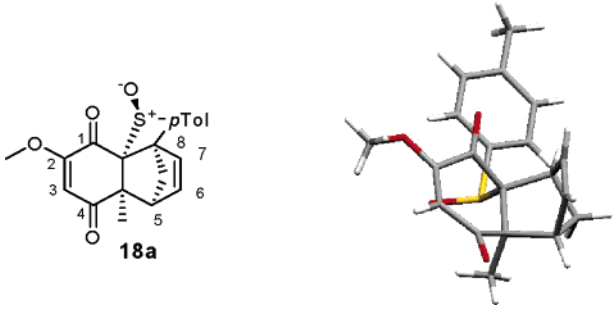


FIGURE 4. X-ray crystal structure of cycloadduct **18a**.

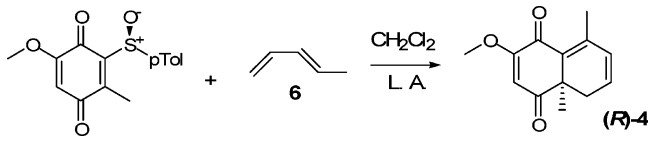
and **6** only at room temperature within few hours. A flash chromatography using demetalated silica gel afforded quantitatively the *p*-tolyl disulfide oxide and the corresponding pyrolized cyclodducts **3** and **4**.

Configurationnal Assignments. The absolute configuration of adduct **18a** has been unambiguously assigned as (4a*S*,5*S*,8*R*,-8a*R)* from its X-ray crystal structure (Figure 4).

The (*R*)-absolute configuration of the angular stereogenic center was confirmed for **3** and **4** from comparison of experimental with calculated VCD/IR spectra of pure samples.[19]

On the basis of the stereochemistry unambiguously assigned to (−)-(*R*)-**3**, (−)-(*R*)-**4**, and (−)-(*R*)-**18a**, the comparison of the different ^{1}H NMR parameters and the previously described model approaches for (S_S)-2-*p*-tolylsulfinyl-1,4-benzoquinone,[6] we established the configuration of **21** as (4a*S*,8*S*,8a*S*). The absolute configuration (4a*S*, 8a*R*) could be assigned to adduct **19a** on the basis of the precedent evidences and ^{1}H−^{1}H NOESY experiments (Figure 5). Assuming that the lone pair of the known (S_S)-sulfinyl moiety was directed to the angular methyl group to minimize steric interaction, and that the corresponding oxygen-atom could not adopt a favorable conformation to allow the stereospecific *syn*-elimination of sulfenic acid (Figure 3),

TABLE 2. Lewis Acid Reaction of Sulfinylquinone 2 in CH_2Cl_2 with 2 equiv of Piperylene 6



entry	Lewis acid	equiv	time	*T* (°C)	isolated yields[a] (%)	ee (%) (abs config)
1	$ZnBr_2$	1	3 days	−20	89	90 (−) (*R*)
2	$ZnBr_2$	2	12 h	−20	92	90 (−) (*R*)
3	$ZnBr_2$	2[b]	4 h	−40	91	95 (−) (*R*)
4	$SnCl_4$	1	12 h	−20	80	60 (−) (*R*)
5	$TiCl_4$	1	4 days	−20	91	97 (−) (*R*)
6	$TiCl_4$	2	1 h	−20	degradation	
7	$BF_3.OEt_2$	1	15 days	−20	49	84 (−) (*R*)
8	$InCl_3$	1	20 days	−20	72	80 (−) (*R*)
9	TMSOTf	1	1.5 h	−78 to −20	degradation	

[a] Isolated yields after purification on demetalated silica gel. The use of standard silica gel decreased the given yields by 12−18%. [b] This reaction has been performed with a large excess of diene (20éq.).

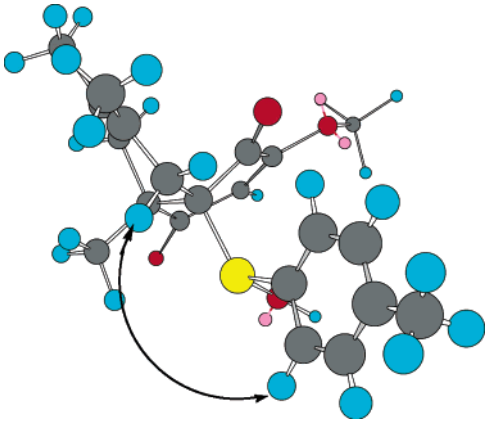


FIGURE 5. NOE observed by the $^1H-^1H$ NOESY experiment of **19a**.

the experimentally observed NOE depicted in Figure 5 was only consistent with (4a*S*,8a*R*) absolute configuration for adduct **19a**. This $^1H-^1H$ NOESY experiment showed a relationship between one of the proton of the methylene α to the sulfinyl group and the more deshielded aromatic protons of the *p*-tolyl group.

The influence of several Lewis acids on the cycloaddition with quinone (S_S)-**2** has also been evaluated. Cycloaddition with diene **6** in dichloromethane at −20 °C has been selected as a probe reaction. In fact, this diene was a good candidate as its cycloaddition occurred with the same stereoselectivity at +20 and −20 °C. For all experiments, quinone (S_S)-**2** and Lewis acid were mixed in dichloromethane at −78 °C and then stirred for10 min before addition of the diene. Finally, the reaction mixture was stored in freezer at −20 °C. The results are summarized in Table 2.

As expected, Lewis acid-catalyzed reactions were always faster than their thermal analogues. Concerning asymmetric induction, the best Lewis acid was $TiCl_4$ (entry 5) used stoechiometrically (97% ee). Nevertheless, the reaction remained quite slow (4 days for total conversion), and the use of 2 equiv of $TiCl_4$ afforded unidentified decomposition products. Finally, $ZnBr_2$ (entries 1−3) proved to be the most efficient Lewis acid. The reaction was much faster (12 h) with 2 equiv of Lewis acid and the good enantioselectivity (90% ee) observed at −20 °C (entry 2) was enhanced up to 95% when the cycloaddition was performed at −40 °C. At this temperature, cycloaddition required longer reaction time but could be reduced to 4 h when

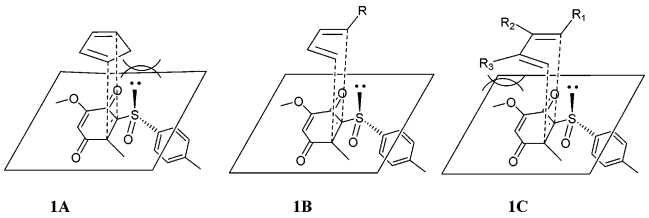


FIGURE 6. Favored approaches of cyclic and acyclic dienes in Diels−Alder reactions of (S_S)-5-methoxy-2-methyl-3-(*p*-tolylsulfinyl)-1,4-benzoquinone **2**.

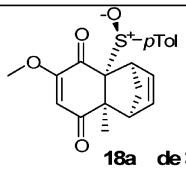
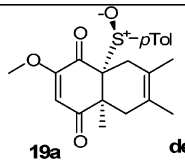
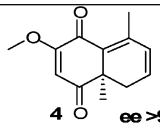
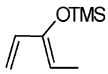
a large excess of diene was used (entry 3). All other tested Lewis acids allowed the formation of the cycloadduct (−)-(*R*)-**4** with moderate π-facial selectivity, except TMSOTf which rapidly destroyed the **(S_s)**-sulfinyl-quinone **2** (entry 9). As we can see, the unvariable sign of the specific rotation of the isolated samples demonstrated that the stereochemical course of the reaction was identical with or without Lewis acids.

The catalytic activity of $ZnBr_2$ was then explored during cycloaddition of the other dienes with (S_S)-sulfinylquinone **2**. With a 1:2:2 (S_S)-**2**/$ZnBr_2$/substrate ratio in dichloromethane at −20 °C, we observed that $ZnBr_2$ caused a dramatic decrease of reaction time and enhanced stereoselectivity to very high level (Table 3). The case of cyclopentadiene (entry 1) illustrated this catalytic activity in a spectacular way. The reaction time was reduced to 2 h and only one cycloadduct (**18a**) was detected in the crude mixture and isolated. In a similar way, cycloadduct **19a** was obtained diastereoselectively as pure product after 12 h (entry 2). Unfortunately, diene **5** was not stable under these conditions, even when stoechiometric amounts of Lewis acid were used.

All the observed stereochemical outcomes in thermal conditions could be rationalized using the transition states previously proposed by Carreño[6,7] where the most favored *endo* approach of the diene occurred from the face of the sulfinylquinone containing the less sterically demanding lone pair at sulfur in the more reactive *s-cis* conformation (Figure 6). Thus, considering the (*R*) absolute configuration induced at the angular methyl group in all cycloadducts, the resulting enantiomers must arise from the attack of the diene on the top face of (S_S)-**2**.

The different diastereoselectivity observed in the cycloaddition of sulfinyl-quinone (S_S)-**2** with cyclic diene **15**, 1-substituted acyclic dienes **6**, **17**, and 2-substituted acyclic diene **5** could be

TABLE 3. $ZnBr_2$ Cycloaddition of Sulfinylquinone 2 with Dienes 5, 6, and 15−17 in CH_2Cl_2

Entry	Diene	Time[c]	Temp.	Isolated yields	Products
1	 15	2 hours	-20°C	98%	 18a de >98%
2	 16	12 hours	-20°C	95%	 19a de >98%
3	 6	12 hours	-20°C	90%	 4 ee >95%
4	 5	30 hours	-78°C	-	Diene degradation

[a] 2 equiv of $ZnBr_2$ was used.

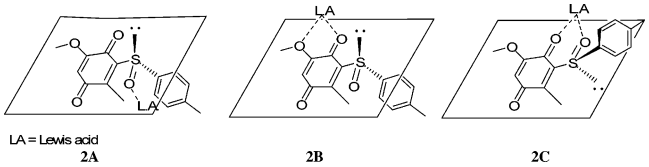


FIGURE 7. Expected major conformations of (S_S)-**2** in the presence of 1 equiv of Lewis acid.

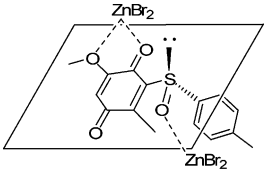


FIGURE 8. Expected major conformation of (S_S)-**2** in the presence of 2 equiv of $ZnBr_2$.

explained by assuming the steric interaction between the methylene bridge of the former or the substituant of the latter with the quinone which develop in the transition state (**1A** and **1C**). This interaction must be more severe with 2,3-disubstituted diene **16** and does not exist with 1-substituted diene (**1B**), which led to the better diastereoselectivity.

The same π-facial diastereoselectivity observed in cycloadditions under thermal or Lewis acid conditions suggested the existence of a similar reactive conformation of the sulfinyl quinonic system in all the cases. This was in sharp contrast with the previously described results obtained with 2-substituted 3-sulfinylquinones lacking the methoxy group at C-5 position which afforded cycloadducts with opposite absolute configuration when the reaction was performed under thermal conditions or in the presence of chelating Lewis acid.[6,7,9,10] A detailed examination of the three possible situations (Figure 7) allowed us to propose that, under Lewis acid conditions and assuming preferred chelation with $ZnBr_2$, **2B** could be the reactive conformation responsible of the favored approach of dienes from the less hindered top face of (S_S)-**2** to afford cycloadducts with the (*R*) absolute configuration at the angular methyl group.

When 2 equiv of $ZnBr_2$ was used, the reaction time decreased and the sign of the specific rotation of isolated cycloadducts remained the same. Assuming the formation of the chelated species **2B** from (S_S)-**2** and 1 equiv of $ZnBr_2$, a bimetallic species such as **2D** should be expected when a second equivalent of Lewis acid was introduced (Figure 8).

Conclusions

In summary, we have reported a large-scale preparation of a new enantiomerically pure sulfinyl quinone as dienophile for highly chemo- and diasteroselective Diels−Alder cycloadditions. This sulfinyl quinone is easily prepared in laboratory in 50-g scale and is stable for years on storage in freezer. The asymmetric synthesis of new enantiopure (ee >97%) Wieland−Miescher-type ketones with differentiated functionalizations of potential interest for the total synthesis of natural products have been presented. Enantiomerically pure building blocks (−)-(*R*)-**3** and (−)-(*R*)-**4** can be prepared in 3 weeks on large scale using very simple conditions and cheap reagents. This delay can be reduced to 2 weeks for (−)-(*R*)-**4** if $ZnBr_2$ is used as catalyst for the cycloaddition step.

Experimental Section

Preparation of (+)-(*S*)S-5-Methoxy-2-methyl-3-(toluene-4-sulfinyl)[1,4]benzoquinone (2). An aqueous solution (720 mL) of ammonium cerium(IV) nitrate (CAN) (68.27 g; 124.52 mmol; 2.5 equiv) was added rapidly (<30 s) to a solution of sulfoxide **13**

(14.46 g; 45.16 mmol; 1.0 equiv) in MeCN (720 mL) at room temperature. After stirring for 40 mn, the ^{1}H NMR analysis indicated that the oxidative demethylation was complete (extended reaction time tends to decrease frankly the yield). The solvent was evaporated and the mixture extracted with CH_2Cl_2 (2 × 400 mL). The combined extracts were washed with water (400 mL) and brine (400 mL) and dried over $MgSO_4$. The solvent was evaporated in a vacuum leaving the sulfinylquinone as an orange solid. Recrystallization of the sulfinylquinone (+)-**2** from boiling MeOH (100 mL) gave pure (+)-**2** (12.049 g; 92%) as bright orange needles. This sulfinylquinone is stable on storage (4−8 °C, protected from light) for more than 2 years. ^{1}H NMR (400 MHz; $CDCl_3$): δ 2.39 (s, 3H); 2.51 (s, 3H); 3.79 (s, 3H); 5.96 (s, 1H); 7.30 (d, ^3J = 8.3 Hz, 2H); 7.64 (d, ^3J = 8.1 Hz, 2H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 9.4; 21.4; 56.5; 107.9; 124.9; 130.1; 139.4; 144.5; 148.1; 157.8;179.1; 185.2. IR (cm^{-1}): 1668; 1626; 1591; 1205. Mp: 133−134 °C (MeOH) (mp racemic: 132−133 °C from MeOH). Anal. Calcd for $C_{15}H_{14}O_4S$: C, 62.05; H, 4.86; S, 11.04. Found: C, 61.89; H, 4.80; S, 11.06. $[\alpha]^{20}_D$ = +445.5 (c = 1.00; CH_2Cl_2)

Preparation of (−)-(*R*)-2-Methoxy-4a,7,8-trimethyl-4α,5-dihydro[1,4]naphthoquinone (4). To a solution of sulfinylquinone (+)-**2** (2 g; 6.9 mmol; 1.0 equiv) in 100 mL of dry CH_2Cl_2, under argon, was added piperylene (mixture of isomers; 1.38 mL; 940 mg; 13.8 mmol; 2.0 equiv). After 10 days at rt, the solvent was evaporated leaving the crude cycloadduct. Flash chromatography on demetalled silica gel (gradient elution 9/1 → 3/1 cyclohexane/EtOAc) afforded pure **(**−**)-4** as a yellow oil (1.42 g, 91%) which crystallized on standing. (Note: chromatography of the reaction mixture using standard silica gel and cyclohexane/EtOAc, 2/1 as eluent afforded **(**−**)-4** in 72−75% yield). ^{1}H NMR (200 MHz; $CDCl_3$): 1.39 (s, 3H); 2.35 (s, 3H); 2.53 (d, J = 2 Hz, 1H); 2.55 (d, J = 1 Hz, 1H); 3.81 (s, 3H); 5.89 (s, 1H); 6.09 (m, 1H); 6.22 (m, 1H). ^{13}C NMR (75 MHz; C_6D_6): δ 21.9; 26.0; 32.8; 45.5; 55.5; 107.7; 129.0; 131.0; 133.3; 145.5; 164.1; 180.9; 199.9. IR (cm^{-1}): 1650; 1602; 1201. TLC R_f: 0.26 (cyclohexane/EtOAc 2/1). Mp: 132 °C. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.58; H, 6.42. Found: C, 71.39; H, 6.31. $[\alpha]^{20}_D$ = −114.5 (c = 0.40; $CHCl_3$).

Preparation of (−)-(*R*)-2-Methoxy-4a,8-dimethyl-7-trimethylsilanyloxy-4a,5-dihydro[1,4]naphthoquinone (14) and (−)-(*R*)-3-Methoxy-5,8a-dimethyl-8,8a-dihydro-7*H*-naphthalene-1,4,6-trione (3). Note: The dienoxysilane **5** can be kept for more than a year under an inert atmosphere at − 20 *τo* +15 °C without apparent decomposition (^{1}H NMR). Nevertheless, before launching the Diels−Alder reaction with sulfinylquinone **2** and a not freshly prepared diene, the latter should be dissolved in Et_2O, washed with a saturated $NaHCO_3$ solution, then with brine, dried over $MgSO_4$, and distilled (50 °C/30 mbar) as a white oil.

To a solution of quinone (+)-**2 (**1.0 g; 3.445 mmol; 1.00 equiv) in 15 mL of dry CH_2Cl_2 under argon was added diene **5** (0.108 g; 6.890 mmol; 2.01 equiv) at −20 °C. The reaction flask was put into the freezer (−20 °C) for 10 days. Flash chromatography on demetallated silica gel (gradient elution 9/1 → 3/1 cyclohexane/EtOAc) afforded pure **(**−**)-14** as a yellow oil (0.960 g, 91%) which crystallized on standing. (Note: chromatography of the reaction mixture using standard silica gel afforded **(**−**)-14** and **(**−**)-4** in only 15 and 20% yield, respectively). ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.26 (s, 9H); 1.29 (s, 3H). 2.29 (s, 3H); 2.53 (d, J = 2 Hz, 1H); 2.55 (d, J = 1 Hz, 1H); 3.82 (s, 3H); 5.35 (m, 1H); 5.91 (s; 1H). ^{13}C NMR (75 MHz; CD_2Cl_2): δ 0.3 ($SiMe_3$); 15.7; 25.3; 31.3; 53.1; 55.1; 107.5; 108.5; 131.4; 145.7; 149.3; 164.0; 180.9; 199.2. IR (cm^{-1}): 1652; 1604; 1536; 1213. TLC R_f: 0.30 (cyclohexane/EtOAc 3/1). Mp: 117−118 °C (Et_2O/pentane). Anal. Calcd for $C_{16}H_{22}O_4Si$: C, 62.75; H, 7.18. Found: C, 62.63; H, 7.39. $[\alpha]^{20}_D$ = −160.7 (c = 0.42; CH_2Cl_2).

A solution of TBAF (1 M in THF 1.633 mL; 1.633 mmol; 1 equiv) was slowly added to a THF (10 mL) solution of **14** (500 mg; 1.633 mmol; 1 equiv) at 0 °C under argon. After 10 min, aqueous ammonium chloride solution (20 mL) was added. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated in a vacuum to give crude **(**−**)-3**. The crude triketone may be purified by flash chromatography on demetalled silica gel (eluent cyclohexane/EtOAc 4/1) or crystallized in Et_2O/pentane at −20 °C to afford pure **(**−**)-3** (363.15 mg; 95% from chromatography or 313.5 mg; 82% from crystallization). ^{1}H NMR (300 MHz; $CDCl_3$): 1.51 (s, 3H); 2.03 (s, 3H); 2.29 (m, 2H); 2.61 (m, 2H); 3.88 (s, 3H); 5.99 (s,1H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 12.8; 26.0; 29.5; 33.4; 49.3; 56.7; 109.4; 138.9; 146.5; 163.1; 185.1; 198.2; 198.5. IR (cm^{-1}): 1656; 1638; 1603; 1154. TLC R_f: 0.21 (cyclohexane/CH_2Cl_2/acetone 10/10/1). Mp: 150 °C (Et_2O/pentane) (mp racemic: 125 °C from Et_2O/pentane). Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.41; H, 5.96. $[\alpha]^{20}_D$ = − 63.5 (c = 0.41; acetone).

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Supporting Information Available: Experimental procedures and spectroscopic and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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