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Reductive Cyclizations of Hydroxysulfinyl Ketones: Enantioselective Access to Tetrahydropyran and Tetrahydrofuran Derivatives

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The stereocontrolled formation of cis-2,5-disubstituted tetrahydrofurans and cis-2,6-disubstituted tetrahydropyrans is achieved from enantiopure ketosulfinyl esters by reduction, Weinreb's amide, and ketone formation, followed by the reductive cyclization (Et_3SiH/TMSOTf) of the resulting hydroxysulfinyl ketones. The sulfoxide-bearing heterocycles were transformed into two natural products, (−)-centrolobine **(1)** and both enantiomers of *cis*-(6-methyltetrahydropyran-2-yl)acetic acid (**2**).

Introduction

2,5-Disubstituted tetrahydrofuran and 2,6-disubstituted tetrahydropyran systems occur in many natural products exhibiting important biological activities.[1] These units can be found in monocyclic and polycyclic structures, fused with carbocyclic or other cyclic ethers, or as spiroketals. The syntheses of such moieties have been achieved through a wide range of methods that have been recently reviewed.[1,2] One of them, the trimethylsilyl triflate catalyzed synthesis of ethers by reductive condensation of carbonyl compounds and alkoxysilanes originally reported by Olah,[3] was later modified by Nicolaou[4] and applied to the intramolecular preparation of cis-2,7-disubstituted oxepane rings from ϵ-hydroxy ketones (Scheme 1, eq 1). Although this approach to cyclic ethers is a stereoselective and high-yielding method, it has been scarcely used in the asymmetric synthesis of tetrahydrofuran and tetrahydropyran derivatives,[5] despite the accessibility of γ- or δ-hydroxyketones necessary as starting materials.

In connection with a program devoted to asymmetric synthesis mediated by sulfoxides,[6] we were interested in the preparation of enantiomerically pure 2,5-disubstituted tetrahydrofuran and 2,6-disubstituted tetrahydropyran derivatives. The key reaction in our synthesis would be the reductive cyclization of the corresponding enantiopure γ-hydroxy-δ-sulfinyl ketones ($n = 1$ in Scheme 1, eq 2) or δ-hydroxy-ϵ-sulfinyl ketones ($n = 2$ in Scheme 1, eq 2), easily accessible through the well-established stereocontrolled reduction of enantiopure β-ketosulfoxides.[7] To know the generality of the stereoselective ring-forming step, we decided to study the reaction not only on aryl ketones which could facilitate the cyclization step but also on alkyl ketones giving rise to dialkyl-substituted derivatives.

In this paper, we present our results showing that the reductive cyclization of hydroxysulfinyl ketones is a short and efficient protocol to enantiopure tetrahydrofuran and tetrahydropyran derivatives. We have previously com-

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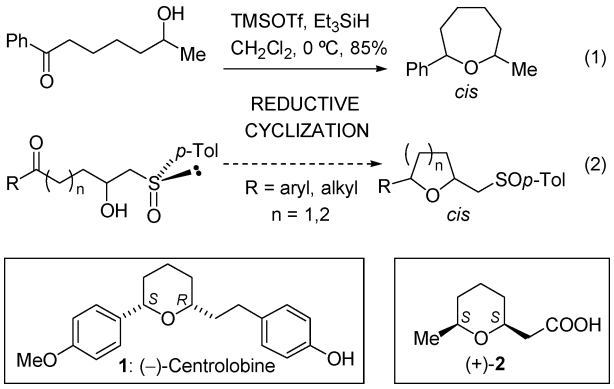
SCHEME 1. Synthesis of Oxygenated Heterocycles from Hydroxy Ketones



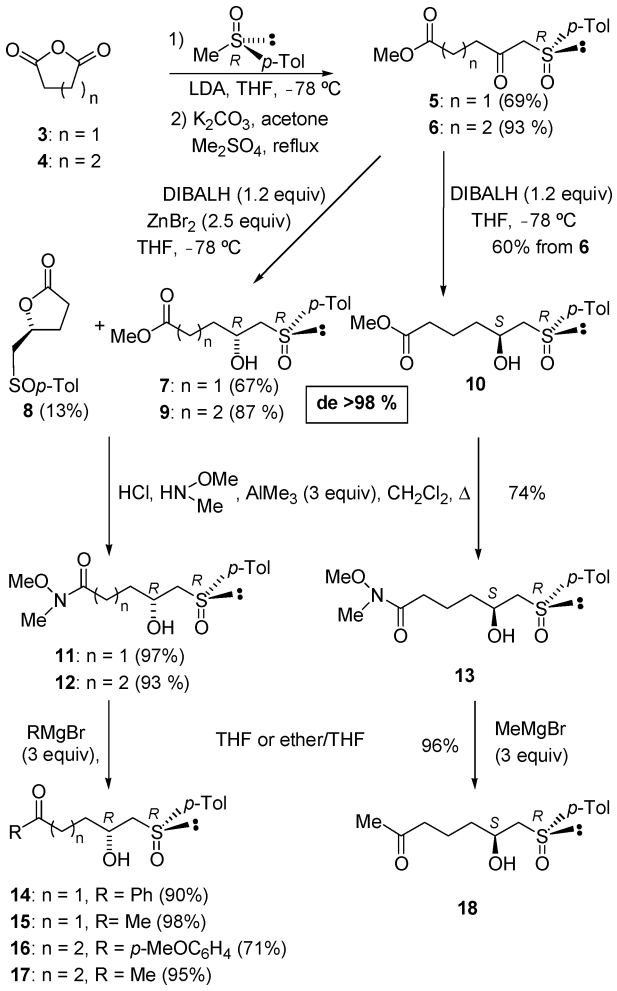
municated the first application of this methodology for the enantioselective synthesis of (−)-centrolobine **(1)**,[8] a natural product bearing a *cis*-2-aryl-6-alkyl-substituted tetrahydropyran skeleton (Scheme 1). We report now a full account of our results as well as a new and diastereodivergent synthesis of (2*S*,6*S*)-*cis*-6-(methyltetrahydropyran-2-yl)acetic acid ((+)-**2**) (Scheme 1),[9] a natural compound isolated from glandular secretions of the civet cat (*Viverra civetta*),[9a] and its unnatural enantiomer (−)-**2**.

Results and Discussion

The synthesis of enantiomerically pure hydroxysulfinyl ketones **14**−**18**, necessary to prepare the oxygenated heterocycles, is shown in Scheme 2. Two important points in our strategy are the use of easily accessible enantiomerically pure *β*-ketosulfoxides[10] **5** and **6**, with an ester function at the terminal position, as starting materials, and the synthesis of Weinreb amides[11] **11**−**13** as versatile intermediates which give easy access to a variety of ketones through the simple and well-established reaction with organometallic reagents.

The synthesis of sulfinyl ketoesters **5** and **6** was achieved by condensation of the lithium anion derived from [(S)*R*]-methyl-*p*-tolylsulfoxide[12] and succinic anhydride (**3**) or glutaric anhydride (**4**) (Scheme 2). Esterification of the resulting acid with dimethyl sulfate in the presence of potassium carbonate gave esters [(S)*R*]-**5** and [(S)*R*]-**6** in 69% and 93% yield, respectively, for the two steps. Although this sequence had been already reported for the reaction with glutaric anhydride,[13] we have improved the overall yield of **6** by working at −78 °C and

SCHEME 2. Stereoselective Synthesis of Hydroxysulfinyl ketones 14−18



modifying the esterification procedure (see the Experimental Section).

Reduction of *β*-ketosulfoxides **5** and **6** with DIBALH in the presence of $ZnBr_2$ afforded *β*-hydroxysulfoxides [*R*,(S)*R*]-**7** (67% yield) and [*R*,(S)*R*]-**9**[13] (87% yield) with an excellent diastereoselectivity (de >98%). In the reaction of compound **5**, a byproduct characterized as 3-[(*p*-tolylsulfinyl)methyl]cyclopentanone (**8**)[14] was isolated in 13% yield. When DIBALH alone was used to reduce the ketosulfinyl ester **6**, compound [*S*,(S)*R*]-**10** was exclusively formed.[15] The *R* absolute configuration at the hydroxylic carbon of **7** and **9**, as well as the *S* absolute configuration of the stereogenic carbon at C-5 of **10**, could be deduced not only from the mechanism already published for the reduction of such *β*-ketosulfoxides[7,16] but also from the ^{1}H NMR spectra of the products. From the numerous examples of reduction of *β*-ketosulfoxides

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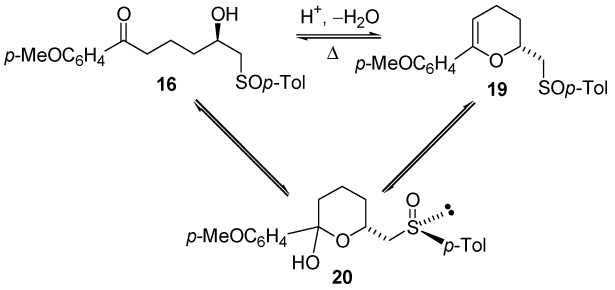
SCHEME 3. Dihydropyran Formation by Acid-Catalyzed Cyclization of Hydroxysulfinyl Ketone 16



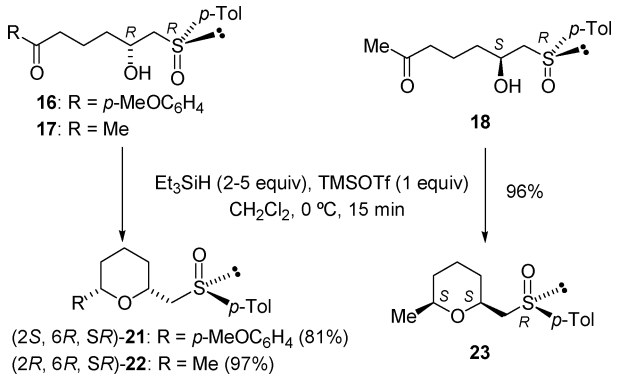
reported, a noticeable difference in the nonequivalence of the methylene hydrogens α to the sulfoxide for the [*R*,(S)*R*] and the [*S*,(S)*R*] epimers has been observed. For the [*R*,(S)*R*] configuration, the $\Delta\nu$ value between these two hydrogens is smaller ($\Delta\nu$ = 49 Hz in **7** and 38 Hz in **9**) than in the [*S*,(S)*R*] diastereomer ($\Delta\nu$ = 96 Hz in **10**). This configurational assignment was essential to revise the absolute configuration of the natural product centrolobine **1**[8] and was confirmed in the case of compounds **9** and **10** by correlation with both known enantiomers of *cis*-6-(methyltetrahydropyran-2-yl)acetic acid **2** (see below).

The synthesis of *N*-methoxy-*N*-methylamides (Weinreb's amides) **11**−**13** was achieved in good to excellent yields (74−97%) by treatment of hydroxysulfinyl esters **7**, **9**, and **10** with *N*-methyl methylhydroxylamine in the presence of an excess of $AlMe_3$ to avoid alcohol protection.[17] Enantiomerically pure hydroxysulfinyl ketones **14**−**18** were finally obtained by reaction of **11**−**13** with an excess of Grignard reagents. Both aryl (R = Ph, *p*-$MeOC_6H_4$) and alkyl (R = Me) magnesium bromides reacted in THF or mixtures of THF/Et_2O to give the corresponding ketones in excellent yields.

The cyclization to the tetrahydropyran ring was first tried by acid-catalyzed acetalization of compound **16** (Scheme 3). The use of *p*-toluenesulfonic acid[18] and camphorsulfonic acid[19] allowed the formation of the cyclic system **19** resulting from the intramolecular acetalization followed by dehydration of the intermediate hemiacetal **20** which could not be detected. In these reactions, 50% of the starting hydroxysulfinyl ketone **16** was recovered unchanged and the 50% isolated yield of dihydropyran **19** could not be improved.

We then turned our attention to the method described by Nicolaou[4] for the reductive cyclization of hydroxy ketones. Thus, treatment of the aryl ketone [5*R*,(S)*R*]-**16** with TMSOTf (1 equiv), followed by an excess of Et_3SiH (2−5 equiv) in CH_2Cl_2 at 0 °C, led to the rapid formation (15 min) of the tetrahydropyran derivative [2*S*,6*R*,(S)*R*]-**21** as a sole diastereomer (Scheme 4).

SCHEME 4. Reductive Cyclization of Hydroxysulfinyl Ketones 16−18



Under the same conditions, cyclization of methyl ketone [5*R*,(S)*R*]-**17** was slower, and after 1 h, the reaction was quenched giving rise to a 60:40 mixture of tetrahydropyran diastereomer **22** and starting material **17**. After flash chromatography, compound [2*R*,6*R*,(S)*R*]-**22** was isolated pure in 43% yield. The behavior of the diastereoisomeric hydroxysulfinyl ketone [5*S*,(S)*R*]-**18** was similar when it was treated with the mixture TMSOTf/Et_3SiH. After 1 h at 0 °C, the reaction was not completed but a clean mixture of [2*S*,6*S*,(S)*R*]-**23** and starting material **18** was detected from which compound **23** could be isolated as a pure diastereomer in 45% yield. We tried to improve these moderate yields by changing the order of addition of the reactants. Indeed, the treatment of methyl ketone [5*R*,(S)*R*]-**17** first with an excess of Et_3SiH (2−5 equiv), followed by the addition of TMSOTf (1 equiv) in CH_2Cl_2 at 0 °C, yielded pure [2*R*,6*R*,(S)*R*]-**22** in an excellent 97% yield. Under the same conditions, the diastereoisomeric hydroxysulfinyl ketone [5*S*,(S)*R*]-**18** gave rise to tetrahydropyran derivative [2*S*,6*S*,(S)*R*]-**23** as a pure diastereomer in 96% yield (Scheme 4). The competitive enolization of the starting hydroxy ketones **17** and **18** under the former conditions could be the origin of the low yield achieved.

The efficiency of this methodology was then checked on hydroxysulfinyl ketones **14** and **15** en route to tetrahydrofuran ring systems. The treatment of aryl ketone [4*R*,(S)*R*]-**14** with an excess of Et_3SiH (2−5 equiv) followed by addition of TMSOTf afforded, after 15 min, a mixture of two isomers, the trans-2,5-disubstituted tetrahydrofuran [2*R*,5*R*,(S)*R*]-**24** and the cis derivative [2*S*,5*R*,(S)*R*]-**25** in a 14:86 ratio from which the cis diastereomer was isolated pure in 71% yield (Scheme 5). The cis substitution of compound **25** was confirmed by NOESY experiments and the relative configuration of the stereogenic carbons of **24** and **25** was determined by *m*-CPBA oxidation of a 50:50 mixture which yielded a 50:50 mixture of sulfones **26** and **27**. A chemical correlation of compound [2*S*,5*R*,(S)*R*]-**25** with tetrahydrofuran derivative (2*S*,5*R*)-**29**, whose (2*R*,5*S*) enantiomer have been recently described,[20] allowed confirmation of its absolute configuration. Thus, compound [2*S*,5*R*,(S)*R*]-**25** was submitted to the Pummerer reaction conditions[21] (TFAA, 2,4,6-collidine) followed by treatment with satu-

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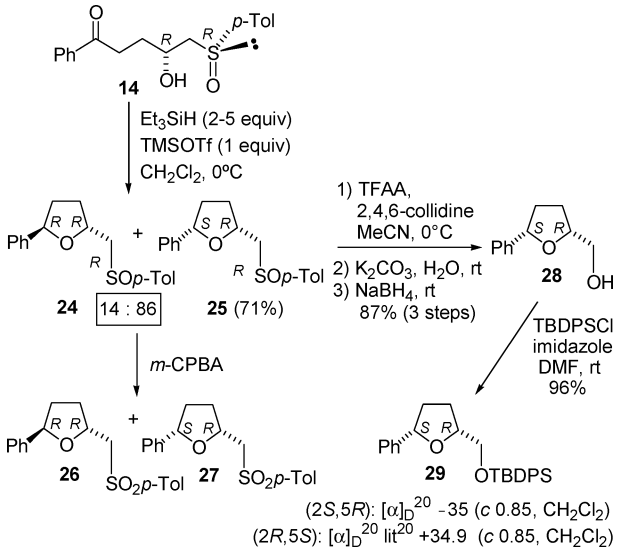
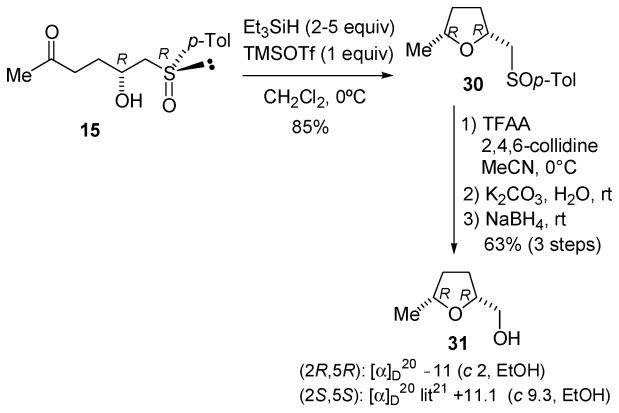
SCHEME 5. Stereoselective Synthesis and Configurational Assignment of Tetrahydrofurans 24 and 25



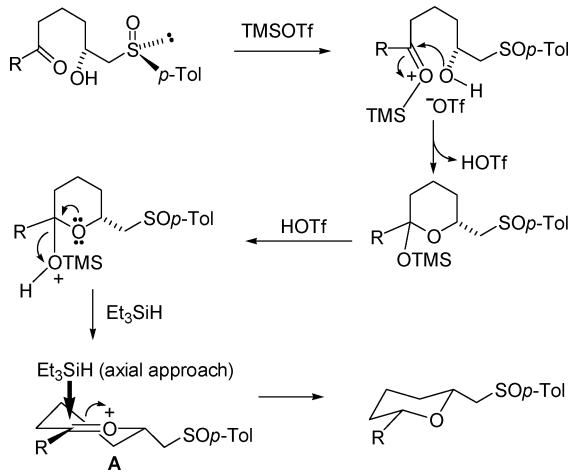
SCHEME 6. Stereoselective Synthesis and Configurational Assignment of Tetrahydrofuran 30



rated aqueous sodium hydrogen carbonate and sodium borohydride. The resulting alcohol (2*S*,5*R*)-**28** (87% yield from **25**) was protected as the TBDPS ether to give tetrahydrofuran (2*S*,5*R*)-**29** in 96% yield. ^{1}H and ^{13}C spectroscopic data of (2*S*,5*R*)-**29** were identical to those previously reported for the (2*R*,5*S*) enantiomer,[20] and the optical rotation [$[\alpha]^{20}_D = -35$ (*c* 0.85, CH_2Cl_2)] was identical but of opposite sign [lit.[20] $[\alpha]^{20}_D = +34.9$ (*c* 0.85, CH_2Cl_2)].

When the aliphatic hydroxysulfinyl ketone **15** was submitted to the same Et_3SiH/TMSOTf treatment, we obtained only the cis diastereomer **30** in 85% yield (Scheme 6). The configuration of [2*R*,5*R*,(S)*R*]-**30** was again confirmed by chemical correlation with the known[22] (2*S*,5*S*) enantiomer of carbinol **31**. Thus, the reductive Pummerer reaction on derivative **30** gave alcohol (2*R*,5*R*)-**31** [$[\alpha]^{20}_D = -11$ (*c* 2, EtOH)], whose spectroscopic parameters were identical to those of its enantiomer but showing the opposite sign of the optical rotation [lit.[22] $[\alpha]^{20}_D = +11.1$ (*c* 9.3, EtOH)]. It is interesting to note

SCHEME 7. Mechanistic and Stereochemical Pathway for the Reductive Cyclization Process



that when aliphatic ketone **15** was first submitted to the addition of TMSOTf followed by Et_3SiH, no cyclization occurred.

A possible mechanistic pathway explaining the major formation of the cis diastereomers in the cyclization step is shown in Scheme 7 for the tetrahydropyran system. Activation of the carbonyl group of the hydroxysulfinyl ketone by the TMSOTf, favors the intramolecular nucleophilic addition of the OH to give an intermediate mixed acetal precursor of the carboxonium intermediate **A**. The axial approach of Et_3SiH[4,23] to **A**, affording the cis diastereomer, is certainly favored because of the higher stability of the resulting chairlike transition state. Similar reasons could explain the major formation of the cis isomer in the case of tetrahydrofurans **25** and **30**.

The application of this efficient methodology to the asymmetric total synthesis of tetrahydropyran natural products from compounds **21**−**23** is illustrated in Schemes 8 and 9, the sulfoxide present in these molecules facilitating further transformations on the side chain to quickly end up the syntheses.

(−)-Centrolobine, 6-[*β*(*p*-hydroxyphenyl)ethyl]-2-(*p*-methoxyphenyl)tetrahydropyran (**1**) (Scheme 8), is a natural product isolated from the heartwood of *Centrolobium robustum*[24] and from the stem of *Brosinum potabile*[25] in the Amazon forest. Although its basic structure was elucidated in 1964 from the total synthesis of the racemic methyl ether,[23a,b] its absolute configuration had not been unequivocally established until 2002, when we reported the first enantioselective total synthesis.[8] Meanwhile, a new asymmetric synthesis of the natural enantiomer based on Prins cyclizations was published by Rychnovsky.[26] Tetrahydropyranylsulfinyl derivative **21** was easily transformed into centrolobine by the synthetic sequence shown in Scheme 8.

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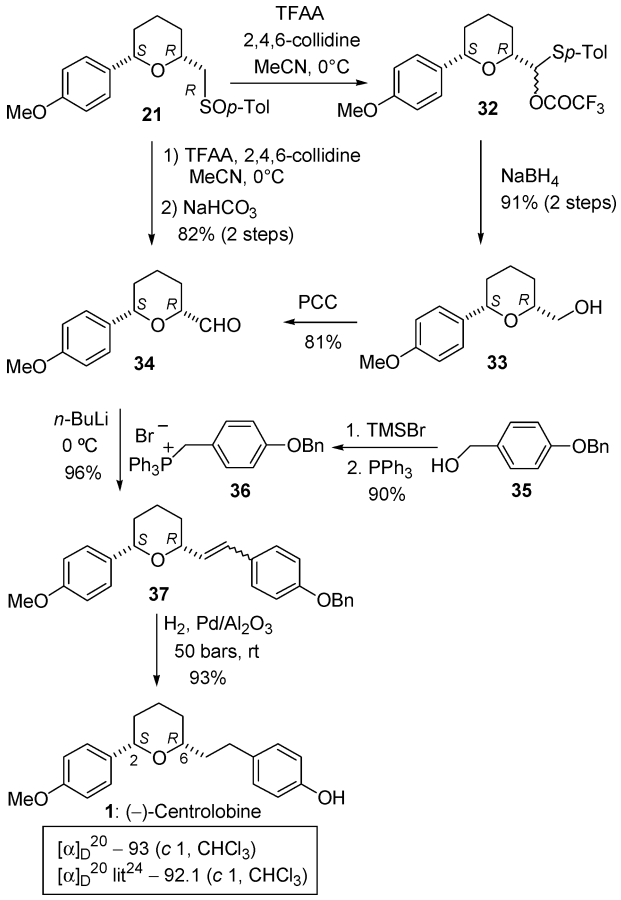
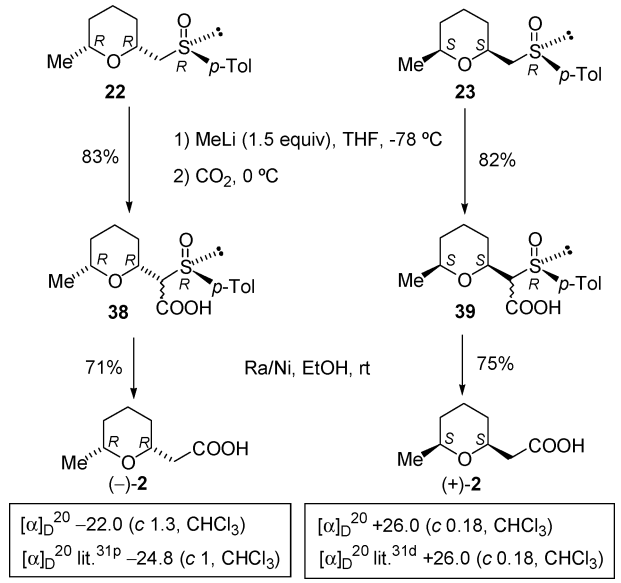
SCHEME 8. Enantioselective Synthesis of (−)-Centrolobine



SCHEME 9. Enantioselective Synthesis of (−)-2 and (+)-2



First, compound **21** was transformed into derivative **32** under the classical TFAA/2,4,6-collidine Pummerer conditions. The reaction of **32** with $NaBH_4$ allowed the preparation of the corresponding alcohol **33** (91% yield from **21**), which, after oxidation in the presence of PCC, yielded aldehyde **34** in 81% yield. A shorter sequence based on the Pummerer rearrangement followed by treatment with saturated aqueous sodium hydrogen carbonate also gave rise to aldehyde **34** (82% yield from **21**). This aldehyde was then submitted to a Wittig reaction with the 4-benzyloxybenzyltriphenylphosphonium salt **36** prepared in 95% overall yield from commercially available 4-benzyloxybenzyl alcohol (**35**), after substitution of the OH by Br[27]and further reaction with PPh_3. The Wittig reaction between 2 equiv of the salt **36** and the aldehyde **34** was carried out in the presence of 2 equiv of BuLi to give the olefin **37** in excellent yield (96%) as a mixture of *E*/*Z* isomers.[28] Finally, simultaneous reduction of the double bond and deprotection of the benzyl ether by catalytic hydrogenation afforded (−)-centrolobine (**1**) in 93% yield.

^1H and ^{13}C NMR and IR spectroscopic data, melting point (95 °C), and optical rotation ($[\alpha]^{20}_D = -93$, *c* 1, $CHCl_3$) of **1** were identical to those described for the natural product.[24,25] De Albuquerque and co-workers[24c] had proposed a (2*R*,6*S*) absolute configuration for (−)-centrolobine **(1)** on the basis of Brewster's empirical rules[29] on the correlation between molecular rotation and absolute configuration. Our synthesis showed that the absolute configuration of (−)-centrolobine **(1)** must be corrected to (2*S*,6*R*), taking into account the [5*R*,(S)*R*] absolute configuration of the precursor *β*-hydroxysulfoxide **16** established considering the well-known behavior of *β*-ketosulfoxide [(S)*R*]-**6** in the reduction with DIBALH/$ZnBr_2$.

Another synthetic application to test the efficiency of this methodology was the asymmetric synthesis of both enantiomers of (*cis*-6-methyltetrahydropyran-2-yl)acetic acid **2** (Scheme 9). The natural enantiomer (+)-(*S*,*S*)-**2**, first isolated by Maurer[9a] from a glandular secretion of the civet cat (*V. civetta*), is highly appreciated as a component of civet, an expensive animal-derived perfume. Several successful synthetic strategies have been reported to access to such simple structure both in the racemic[9a,23,30] and optically enriched forms.[31] Our highly stereoselective synthetic strategy combining reduction of a *β*-ketosulfoxide with the reductive cyclization of a hydroxysulfinyl ketone afforded compounds **22** and **23** which were transformed in two steps into both enantiomers of **2** (Scheme 9).

First, reaction of the α-sulfinyl carbanion resulting in the treatment of **22** or **23** with MeLi and CO_2 gave carboxylic acids **38** (83% yield) or **39** (82% yield), which

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(29) Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5481−5493.
(30) (a) Banwell, M. G.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 967−969. (b) Muraoka, O.; Okumura, M.; Maeda, T.; Wang, L.; Tanabe, G. *Chem. Pharm. Bull.* **1995**, *43*, 517−519. (c) Varelis, P.; Graham, A. J.; Johnson, B. L.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1994**, *47*, 1735−1739. (d) Lee, E., Jin, S., Lee, C. *Tetrahedron Lett.* **1993**, *34*, 4831−4834. (e) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990**, *46*, 4595−4612. (f) Homma, K.; Mukaiyama, T. *Chem. Lett.* **1989**, 893−896. (g) Kobayashi, K.; Suginome, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 951−952. (h) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron Lett.* **1987**, *28*, 6613−6616. (i) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911−913. (j) Nussbaumer, C.; Frater, G. *Helv. Chim. Acta* **1987**, *70*, 396−401. (k) Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1554−1555. (l) Ley, S.; Lygo, B.; Molines, H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2403−2405. (m) Bates, H. A.; Deng, P. *J. Org. Chem.* **1983**, *48*, 4479−4481. (n) Ley, S.; Lygo, B.; Molines, H.; Morton, J. A. *J. Chem. Soc., Chem. Commun.* **1982**, 1521−1522. (o) Kim, Y.; Mundy, B. P. *J. Org. Chem.* **1982**, *47*, 3556−3557.

were characterized as a 1:1 mixture of two epimers at the carbon α to the carboxylic acid (Scheme 8). Each diastereoisomeric mixture was submitted to desulfurization with Ra/Ni to obtain each enantiomer of *cis*-(6-methyltetrahydropyran-2-yl)acetic acid ((−)-(2*R*,6*R*)-**2** (71%) and (+)-(2*S*,6*S*)-**2** (75%)). The final comparison of the $[\alpha]^{20}_D$ value of (+)-(2*S*,6*S*)-**2** with that of the natural enantiomer confirmed again the configurational assignment previously established for the precursor **23** on the basis of the mechanism of the *β*-ketosulfoxides reductions and the spectroscopic parameters of the *β*-hydroxysulfoxides **9** and **10**.

Conclusions

We have reported a highly enantioselective approach to cis-2,5-disubstituted tetrahydrofuran and 2,6-disubstituted tetrahydropyran systems combining two efficient processes: the stereocontrolled reduction of enantiopure *β*-ketosulfoxides and the reductive cyclization of hydroxysulfinyl ketones easily accessible from the former. The yield of the cyclization step strongly depends on the sense of addition of the reactants. The best yields were obtained by adding first the Et_3SiH on the solution containing the hydroxysulfynilketone, followed by TMSOTf. The methodology is highly versatile due to the intermediate formation of a heterocyclic system bearing a sulfoxide which facilitates further functionalization. Application to the enantioselective synthesis of natural products has given rise to the efficient asymmetric synthesis of (−)-centrolobine **(1)** (nine steps and 32% overall yield from glutaric anhydride) and both enantiomers of *cis*-(6-methyltetrahydropyran-2-yl)acetic acid **2** [eight steps, 41% overall yield for (−)-(2*R*,6*R*)-**2** and 24% overall yield for (+)-(2*S*,6*S*)-**2** from glutaric anhydride].

Experimental Section

General Procedure for the Synthesis of Ketosulfinyl Esters. Method A. The synthesis of compounds **5** and **6** was carried out by following our previously reported procedure[13] modified as follows: To a solution of LDA (2.1 equiv) in THF was added a solution of [(S)*R*]-methyl-*p*-tolylsulfoxide[12] (2 equiv for **5**; 1 equiv for **6**) in THF (0.75 M) dropwise at −78 °C, under argon. After the mixture was stirred for 90 min, a solution of the corresponding anhydride **3** or **4** (1 equiv) in THF (0.9 M) was slowly added. The resulting mixture was stirred at −78 °C for 2 h, and a saturated NH_4Cl aqueous solution was added. The aqueous phase was extracted with EtOAc to eliminate the remaining methyl-*p*-tolylsulfoxide and acidified with 1 M HCl. After extraction with ethyl acetate and workup, the crude ketosulfinyl carboxylic acid was obtained. The acid was dissolved in acetone (0.9 M) and added to a solution of anhydrous K_2CO_3 (1.1 equiv) in acetone (1.6 M) at rt. The reaction mixture was stirred for 5 min, and dimethyl sulfate (1.1 equiv) was added. The solution was refluxed for 2 h, cooled, filtered, and concentrated under reduced pressure. Purification was effected as indicated in each case.

Methyl [(S)*R*]-4-Oxo-5-(*p*-tolylsulfinyl)pentanoate (5). Compound **5** was obtained from succinic anhydride (**3**) following method A, after purification by flash chromatography (eluent EtOAc), as a white solid, in 69% yield: mp 91−92 °C; $[\alpha]^{20}_D$ +185 (*c* 1, $CHCl_3$); ^{1}H NMR *δ* 7.52 and 7.32 (4H, AA′BB′ system), 3.88 and 3.80 (2H, AB system, *J* = 13.4 Hz), 3.65 (3H, s), 2.80 (2H, m), 2.56 (2H, t, *J* = 6.2 Hz), 2.41 (3H, s); ^{13}C NMR *δ* 199.8, 172.7, 142.2, 139.6, 130.2, 124.0, 68.0, 51.9, 39.5, 27.5, 21.7.

Methyl [(S)*R*]-5-Oxo-6-(*p*-tolylsulfinyl)hexanoate (6). Compound **6** was obtained from glutaric anhydride (**4**) following method A as a white solid, in 93% yield: mp 45 °C (lit.[13] mp 45−47 °C); $[\alpha]^{20}_D$ +192 (*c* 1, acetone) [(lit.[13] $[\alpha]^{20}_D$ +195 (*c* 1, acetone)]; ^{1}H NMR *δ* 7.50 and 7.31 (4H, AA′BB′ system), 3.82 and 3.72 (2H, AB system, *J* = 13.2 Hz), 3.63 (3H, s), 2.59 (2H, m), 2.42 (3H, s), 2.30 (2H, t, *J* = 7.2 Hz), 1.85 (2H, m); ^{13}C NMR *δ* 200.6, 173.1, 141.9, 139.3, 129.8, 123.8, 67.5, 51.3, 43.5, 32.3, 21.6, 17.9.

General Procedure for the $ZnBr_2$-Mediated Reductions of Ketosulfinyl Esters. Method B. A solution of the corresponding *β*-ketosulfoxide **5** or **6** (7.7 mmol) and dry zinc bromide (11.6 mmol) in THF (100 mL) was stirred at rt for 90 min and cooled to −78 °C. DIBALH (9.5 mL of a 0.9 M solution in heptane, 8.5 mmol) was added dropwise for 2 h, and the resulting mixture was stirred at −78 °C for 30 min and quenched by addition of a saturated solution of sodium tartrate. After extraction with EtOAc and workup, the crude mixture was purified by flash chromatography.

Methyl [4*R*,(S)*R*]-4-Hydroxy-5-(*p*-tolylsulfinyl)pentanoate (7). Reduction of compound **5** following method B afforded a crude mixture which after flash chromatography (eluent EtOAc) gave starting material **5** in 16% yield, 3-[(*p*-tolylsulfinyl)methyl]cyclopentanone (**8**)[14] in 13% yield, and alcohol **7** as a white solid, in 67% yield: mp 68−69 °C; $[\alpha]^{20}_D$ +212 (*c* 1, $CHCl_3$); ^{1}H NMR *δ* 7.56 and 7.32 (4H, AA′BB′ system), 3.63 (3H, s), 4.07, 3.12 and 2.84 (3H, ABX system, *J* = 13.4, 8.1, 3.8 Hz), 2.48 (2H, m), 2.40 (3H, s), 1.89 (2H, m); ^{13}C NMR *δ* 173.5, 141.5, 139.8, 129.8, 123.7, 66.5, 63.0, 51.3, 31.4, 29.3, 21.1; MS (EI) *m*/*z* 270 (M^+, 0.1), 238 (11), 222 (5), 139 (100), 115 (8), 99 (36), 77 (12), 65 (20); HRMS (EI) calcd for $C_{13}H_{18}O_4S$ (M^+) 270.0926, found 270.0924.

Methyl [5*R*,(S)*R*]-5-Hydroxy-6-(*p*-tolylsulfinyl)hexanoate (9). Compound **9** was obtained from **6** following method B, after flash chromatography (eluent EtOAc) as a white solid, in 87% yield: mp 46 °C (lit.[13] mp 46−47 °C); $[\alpha]^{20}_D$ +180 (*c* 1, $CHCl_3$) [lit.[13] $[\alpha]^{20}_D$ +178 (*c* 1, $CHCl_3$)]; ^{1}H NMR *δ* 7.54 and 7.33 (4H, AA′BB′ system), 3.91 (1H, br s), 3.66 (3H, s), 4.30, 2.99 and 2.78 (3H, ABX system, *J* = 12.9, 9.1, 2.6 Hz), 2.42 (3H, s), 2.35 (2H, t, *J* = 7 Hz), 1.8−1.5 (4H, m); ^{13}C NMR *δ* 174.3, 142.5, 140.9, 130.6, 124.3, 68.7, 62.8, 52.0, 36.8, 33.9, 20.8, 21.8.

Methyl [5*S*,(S)*R*]-5-Hydroxy-6-(*p*-tolylsulfinyl)hexanoate (10). DIBALH (4.0 mL of a 1 M solution in toluene, 4.0 mmol) was added dropwise to a solution of the *β*-ketosulfoxide **6** (0.9 g, 3.2 mmol) in THF (30 mL) at −78 °C. The solution was stirred at −78 °C for 90 min, quenched with methanol (10 mL), and concentrated under reduced pressure. The residue was diluted with EtOAc and acidified with 1 M HCl. After extraction with EtOAc, workup, and flash chromatography (eluent EtOAc), compound **10** was obtained as a white solid, in 60% yield: mp 80 °C (lit.[15] mp 80−82 °C); $[\alpha]^{20}_D$ +231 (*c* 0.9, $CHCl_3$) [lit.[15] $[\alpha]^{20}_D$ +232 (c 0.9, $CHCl_3$)]; ^{1}H NMR *δ* 7.50 and 7.36 (4H,

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AA′BB′ system, $J = 8.1$ Hz), 3.65 (3H, s), 4.20, 2.93 and 2.75 (3H, ABX system, $J = 13.4$, 9.9, 2.1 Hz), 2.42 (3H, s), 2.30 (2H, t, $J = 7$ Hz), 1.8−1.4 (4H, m); ^{13}C NMR δ 174.1, 141.7, 139.4, 130.2, 124.1, 66.3, 61.2, 51.7, 36.4, 33.6, 21.5, 20.5.

General Procedure for the Synthesis of Weinreb's Amides. Method C. A solution of $AlMe_3$ (3.6 mL of a 2 M solution in toluene, 7.2 mmol) was added dropwise at rt to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (718 mg, 7.2 mmol) in CH_2Cl_2 (20 mL). After the mixture was stirred for 30 min, a solution of the corresponding ketosulfinyl ester (2.4 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was refluxed for 4 h, cooled, and quenched with 0.5 M HCl. After workup, the pure amide was obtained.

[4*R*,(S)*R*]-*N*-Methoxy-*N*-methyl-4-hydroxy-5-(*p*-tolylsulfinyl)pentanamide (11). Compound **11** was obtained from **7** following method C as a yellowish oil, in 97% yield: $[\alpha]^{20}_D$ +156 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.54 and 7.32 (4H, AA′BB′ system), 4.37 (1H, br s), 3.69 (3H, s), 3.18 (3H, s), 4.26, 2.97 and 2.85 (3H, ABX system, $J = 13.2$, 8.8, 2.9 Hz), 2.60 (2H, m), 2.41 (3H, s), 1.88 (2H, m); ^{13}C NMR δ 174.7, 141.8, 140.9, 130.0, 124.0, 67.9, 63.0, 61.2, 32.1, 31.4, 27.6, 21.4; MS (EI) *m*/*z* 299 (M^+, 0.2), 238 (8), 160 (17), 139 (100), 123 (9), 99 (32), 77 (11), 65 (17); HRMS (EI) calcd for $C_{14}H_{21}O_4S$ (M^+) 299.1191, found 299.1178.

[5*R*,(S)*R*]-*N*-Methoxy-*N*-methyl-5-hydroxy-6-(*p*-tolylsulfinyl)hexanamide (12). Compound **12** was obtained from **9** following method C as a yellow oil, in 93% yield: $[\alpha]^{20}_D$ +139 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.53 and 7.32 (4H, AA′BB′ system), 4.07 (1H, br s), 3.66 (3H, s), 3.16 (3H, s), 4.24, 2.97 and 2.78 (3H, ABX system, $J = 13.1$, 9.2, 2.7 Hz), 2.41 (3H, s), 2.46 (2H, m), 1.9−1.5 (4H, m); ^{13}C NMR δ 174.7, 142.3, 140.9, 130.5, 124.4, 68.3, 63.4, 61.6, 32.4, 36.9, 31.6, 30.2, 21.8; MS (EI) *m*/*z* 313 (M^+, 0.7), 253 (16), 174 (16), 139 (100), 113 (42), 85 (27), 67 (18); HRMS (EI) calcd for $C_{15}H_{23}NO_4S$ (M^+) 313.1348, found 313.1335. Anal. Calcd for $C_{15}H_{23}NO_4S$: C, 57.19; H, 7.36. Found: C, 57.24; H, 7.36.

***N*-Methoxy-*N*-methyl-[5*S*,(S)*R*]-5-hydroxy-6-(*p*-tolylsulfinyl)hexanamide (13).** Compound **13** was obtained from **10** following method C as a yellow oil, in 74% yield: $[\alpha]^{20}_D$ +178 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.52 and 7.32 (4H, AA′BB′ system), 4.85 (1H, br s), 3.66 (3H, s), 3.16 (3H, s), 4.21, 2.94 and 2.75 (3H, ABX system, $J = 13.4$, 9.9, 2.1 Hz), 2.45 (2H, t, $J = 7$ Hz), 2.41 (3H, s), 1.8−1.4 (4H, m); ^{13}C NMR δ 174.0, 141.1, 139.9, 129.7, 123.7, 65.1, 63.6, 60.9, 36.4, 31.8, 31.0, 29.7, 21.1; MS (EI) *m*/*z* 313 (M^+, 0.2), 253 (9), 156 (13), 139 (100), 126 (25), 113 (31), 91 (54), 69 (17); HRMS (EI) calcd for $C_{15}H_{23}NO_4S$ (M^+) 313.1348, found 313.1346.

General Procedure for the Synthesis of Hydroxysulfinyl Ketones. Method D. A solution of the corresponding Grignard reagent in ether or THF (1.0 mmol) was added to a solution of Weinreb's amide (1.0 mmol) in THF (10 mL) at rt, under argon. The reaction mixture was stirred for 1−2 h at rt and quenched with saturated NH_4Cl. After workup and flash chromatography, pure keto hydroxy sulfoxides were obtained.

[4*R*,(S)*R*]-4-Hydroxy-1-phenyl-5-(*p*-tolylsulfinyl)pentanone (14). Compound **14** was obtained from amide **11** and PhMgBr in ether following method D (eluent EtOAc) as a white solid, in 90% yield: mp 98−99 °C; $[\alpha]^{20}_D$ +187 (*c* 1, $CHCl_3$); ^{1}H NMR δ 8.0−7.3 (9H, m), 4.13 (1H, br s), 3.20 (2H, t, $J = 7$ Hz), 4.43, 2.99 and 2.84 (3H, ABX system, $J = 12.9$, 9.1, 2.2 Hz), 2.42 (3H, s), 1.99 (2H, m); ^{13}C NMR δ 199.99, 142.09, 140.28, 136.68, 133.17, 130.19, 128.57, 128.07, 123.94, 68.05, 62.55, 33.99, 31.15, 21.42; MS (EI) *m*/*z* 298 (M^+ − 18, 0.5), 282 (24), 158 (53), 137 (43), 124 (26), 105 (70), 84 (100).

[5*R*,(S)*R*]-5-Hydroxy-6-(*p*-tolylsulfinyl)hexan-2-one (15). Compound **15** was obtained from amide **11** and MeMgBr in ether following method D as a colorless oil, in 98% yield, and used without further purification: $[\alpha]^{20}_D$ +177 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.51 and 7.30 (4H, AA′BB′ system), 4.23, 2.94 and 2.82 (3H, ABX system, $J = 13.4$, 9.1, 2.7 Hz), 2.62 (2H, t, $J = 7$ Hz), 2.39 (3H, s), 2.13 (3H, s), 1.80 (2H, m); ^{13}C NMR δ 208.7, 142.0, 140.3, 130.1, 123.8, 67.8, 62.5, 38.9, 30.6, 29.6, 21.4; MS (EI) *m*/*z* 236 (M^+ − 18, 6), 220 (16), 154 (16), 137 (100), 124 (29), 97 (68), 84 (92), 65 (34).

[5*R*,(S)*R*]-5-Hydroxy-1-(*p*-methoxyphenyl)-6-(*p*-tolylsulfinyl)hexanone (16). Compound **16** was obtained from amide **12** and *p*-methoxyphenylmagnesium bromide in ether following method D, stirring the mixture at 50 °C (eluent EtOAc followed by EtOAc/MeOH 10:1), as an oil, in 71% yield: $[\alpha]^{20}_D$ +127 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.92 and 6.91 (4H, AA′BB′ system), 7.53 and 7.31 (4H, AA′BB′ system), 3.98 (1H, br s), 3.86 (3H, s), 2.97 (2H, t, $J = 7$ Hz), 4.29, 2.97 and 2.86 (3H, ABX system, $J = 13.2$, 8.9, 2.7 Hz), 2.41 (3H, s), 2.0−1.6 (4H, m); ^{13}C NMR δ 199.1, 163.9, 142.4, 140.9, 130.5, 130.7, 130.3, 124.4, 114.1, 68.7, 62.9, 55.9, 38.0, 37.0, 21.8, 20.1. Anal. Calcd for $C_{20}H_{24}O_4S$: C, 66.32; H, 6.71. Found: C, 66.07; H, 6.63.

[6*R*,(S)*R*]-6-Hydroxy-7-(*p*-tolylsulfinyl)heptan-2-one (17). Compound **17** was obtained from amide **12** and MeMgBr following method D as a white solid, in 95% yield: mp 58−59 °C; $[\alpha]^{20}_D$ +157 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.50 and 7.29 (4H, AA′BB′ system), 4.16, 2.94 and 2.73 (3H, ABX system, $J = 12.9$, 9.1, 2.7 Hz), 2.43 (2H, t, $J = 6.9$ Hz), 2.38 (3H, s), 2.09 (3H, s), 1.7−1.1 (4H, m); ^{13}C NMR δ 208.8, 142.0, 140.6, 130.2, 129.8, 124.5, 123.9, 68.4, 62.2, 43.1, 36.4, 29.9, 21.4, 19.0; MS (EI) *m*/*z* 268 (M^+, 0.3), 251 (4), 233 (11), 140 (100), 129 (28), 111 (49), 92 (71), 77 (14), 71 (64); HRMS (EI) calcd for $C_{14}H_{20}O_3S$ (M^+) 268.1133, found 268.1126.

[6*S*,(S)*R*]-6-Hydroxy-7-(*p*-tolylsulfinyl)heptan-2-one (18). Compound **18** was obtained from amide **13** and MeMgBr following method D as a colorless oil, in 96% yield: $[\alpha]^{20}_D$ +220 (*c* 1.16, $CHCl_3$); ^{1}H NMR δ 7.48 and 7.29 (4H, AA′BB′ system), 4.69 (1H, br s), 4.14, 2.92 and 2.67 (3H, ABX system, $J = 13.4$, 9.9, 2.1 Hz), 2.41 (2H, t, $J = 6.9$ Hz), 2.38 (3H, s), 2.07 (3H, s), 1.8−1.1 (4H, m); ^{13}C NMR δ 208.8, 141.5, 139.4, 130.0, 123.9, 66.1, 61.4, 43.0, 36.3, 29.9, 21.4, 19.0; MS (EI) *m*/*z* 250 (M^+ − 18, 5), 247 (10), 233 (17), 163 (7), 139 (100), 124 (52), 91 (99), 77 (34).

General Procedure for the Reductive Cyclizations of Hydroxysulfinyl Ketones. Method E. To a solution of the corresponding hydroxysulfinyl ketone (1.12 mmol) in CH_2Cl_2 (30 mL) was added dropwise Et_3SiH (360 μL, 2.24 mmol) at 0 °C, followed by TMSOTf (264 μL, 1.45 mmol). The mixture was stirred for 15 min at 0 °C and quenched with water. After workup and flash chromatography, pure tetrahydropyran or tetrahydrofuran derivatives were obtained.

[2*S*,6*R*,(S)*R*]-2-(*p*-Methoxyphenyl)-6-[(*p*-tolylsulfinyl)-methyl]tetrahydropyran (21). Compound **21** was obtained from **16** following method E (eluent EtOAc) as a white solid, in 92% yield: mp 127 °C; $[\alpha]^{20}_D$ −71 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.55 and 7.30 (4H, AA′BB′ system), 7.23 and 6.88 (4H, AA′BB′ system), 4.20 (1H, m), 3.79 (3H, s), 3.63, 3.33 and 2.86 (3H, ABX system, $J = 13.2$, 7.1, 5.2 Hz), 2.38 (3H, s), 2.0−1.4 (6H, m); ^{13}C NMR δ 159.3, 141.9, 140.8, 135.2, 130.2, 127.3, 124.8, 114.0, 79.8, 73.3, 63.8, 55.7, 33.3, 31.0, 24.0, 21.8. Anal. Calcd for $C_{20}H_{24}O_3S$: C, 69.15; H, 7.02. Found: C, 68.80; H, 6.95.

[2*R*,6*R*,(S)*R*]-2-Methyl-6-[(*p*-tolylsulfinyl)methyl]tetrahydropyran (22). Compound **22** was obtained from **17** following method E (eluent EtOAc) as a colorless oil, in 97% yield: $[\alpha]^{20}_D$ +47 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.53 and 7.29 (4H, AA′BB′ system), 3.25 (1H, m), 3.41, 3.23 and 2.71 (3H, ABX system, $J = 12.9$, 7.5, 4.8 Hz), 2.40 (3H, s), 1.8−1.2 (6H, m), 1.08 (3H, d, $J = 6.1$ Hz); ^{13}C NMR δ 141.4, 140.4, 129.7, 124.3, 74.0, 72.3, 63.3, 32.6, 30.5, 23.1, 21.8, 21.4; MS (EI) *m*/*z* 252 (M^+, 7), 140 (57), 113 (100), 95 (53), 69 (40); HRMS (EI) calcd for $C_{14}H_{20}O_2S$ (M^+) 252.1184, found 252.1174.

[2*S*,6*S*,(S)*R*]-2-Methyl-6-[(*p*-tolylsulfinyl)methyl]tetrahydropyran (23). Compound **23** was obtained from **18** following method E (eluent EtOAc) as a colorless oil, in 96% yield: $[\alpha]^{20}_D$ +232 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.54 and 7.30 (4H, AA′BB′ system), 3.96 (1H, m), 3.59 (1H, m), 2.77 (2H, m), 2.40 (3H, s), 1.9−1.4 (6H, m), 1.22 (3H, d, $J = 6.3$ Hz); ^{13}C NMR δ 141.6, 141.1, 129.8, 123.7, 74.0, 71.1, 65.1, 32.7, 30.9, 23.3, 21.8, 21.2; MS (EI) *m*/*z* 252 (M^+, 8), 140 (61), 127 (7), 113 (100), 95

(56), 81 (26), 69 (44); HRMS (EI) calcd for $C_{14}H_{20}O_2S$ (M^+) 252.1184, found 252.1176.

[2*S*,5*R*,(S)*R*]-2-Phenyl-5-[(*p*-tolylsulfinyl)methyl]tetrahydrofuran (25). Compound **25** was obtained from **14** following method E, as a 1:6 mixture of diastereoisomers **24** and **25** from which **25** was isolated pure by flash chromatography (eluent EtOAc/hexane 3:1) as a white solid, in 71% yield: mp 93−94 °C; $[\alpha]^{20}_D$ −27 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.6−7.2 (9H, m), 4.87 (1H, t, J = 7 Hz), 4.14 (1H, m), 3.26 and 2.97 (2H, ABX system, part AB, J = 12.9, 6.5, 5.9 Hz), 2.41 (3H, s), 2.3−1.8 (4H, m); ^{13}C NMR δ 142.2, 141.8, 140.3, 130.0, 128.1, 127.5, 125.7, 124.3, 81.5, 74.0, 62.84, 34.2, 31.1, 21.6; MS (EI) *m*/*z* 300 (M^+, 0.6), 284 (9), 161 (95), 140 (31), 117 (69), 105 (30), 91 (100), 77 (29); HRMS (EI) calcd for $C_{18}H_{20}O_2S$ (M^+) 300.1184, found 300.1172.

2-Phenyl-5-[(*p*-tolylsulfonyl)methyl]tetrahydrofuran (26 and 27). A solution of compounds **24** and **25** (50:50 mixture, 18 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) was treated with *m*-CPBA (0.12 mmol) at rt. The mixture was stirred for 30 min and washed with saturated $NaHCO_3$. After workup, a 50:50 mixture of sulfones **26** and **27** was obtained as a white solid, in 95% yield: ^{1}H NMR δ 7.6−7.2 (9H, m), 4.9−4.7 (1H, m), 4.4−4.6 (1H, m), 3.53 and 3.27 (1H, part AB of ABX system, J = 14.0, 5.9, 6.5 Hz), 3.55 and 3.28 (1H, part AB of ABX system, J = 14.0, 5.9, 6.5 Hz), 2.41 (3H, s), 2.3−1.8 (4H, m); ^{13}C NMR δ 145.1, 143.0, 137.5 (3C), 130.6, 130.2, 128.7, 127.7, 125.8 (9C), 81.5, 74.1, 62.2, 34.9, 32.9, 22.1, 145.1, 142.4, 137.3 (3C), 130.5, 130.2, 128.6, 127.7, 125.8 (9C), 80.9, 74.0, 61.9, 34.0, 31.9, 22.0.

(2*S*,5*R*)-2-Phenyl-5-(hydroxymethyl)tetrahydrofuran (28). To a solution of **24** (651 mg, 2.2 mmol) and 2,4,6-collidine (868 μL, 6.6 mmol) in CH_3CN (25 mL) was added trifluoroacetic anhydride (1.54 mL, 10.8 mmol) at 0 °C. After the mixture was stirred at 0 °C for 10 min, water (3 mL) was added, and the resulting solution was neutralized with solid K_2CO_3. After the solution was stirred for 30 min, an excess of $NaBH_4$ (410 mg, 10.8 mmol) was added. The mixture was stirred for 1 h at rt and quenched at 0 °C with saturated NH_4Cl. The solution was extracted with EtOAc and washed with 1 M HCl, saturated $NaHCO_3$, and brine. After workup and flash chromatography (eluent EtOAc/hexane 1:1), compound **28** was obtained as a colorless oil, in 87% yield: $[\alpha]^{20}_D$ −52 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.34 (5H, m), 4.92 (1H, t, J = 7 Hz), 4.20, 3.80 and 3.65 (3H, ABX system, J = 11.5, 2.8, 6.0 Hz), 2.4−1.8 (4H, m); ^{13}C NMR δ 142.4, 128.4, 127.5, 125.9, 81.5, 80.00, 65.4, 34.5, 27.6.

(2*S*,5*R*)-2-Phenyl-5-[(*tert*-butyldiphenylsilyloxy)methyl]tetrahydrofuran (29). To a solution of **28** (200 mg, 1,12 mmol) in dry DMF (5 mL) at rt, imidazole (170 mg, 2.47 mmol) and TBDPSCl (328 μL, 1.23 mmol) were slowly added. The mixture was stirred for 1 h at rt and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and washed with water and brine. After workup and flash chromatography (eluent EtOAc/hexane 1:16), compound **29** was obtained as a colorless oil, in 96% yield: $[\alpha]^{20}_D$ −35 (*c* 0.86, CH_2Cl_2); ^{1}H NMR δ 7.72 (4H, m), 7.4−7.2 (11H, m), 4.91 (1H, dd, J = 6.4 and 8.3 Hz), 4.22 (1H, m), 3.81 (2H, d, J = 4.6 Hz), 2.3−1.7 (4H, m), 1.08 (9H, s); ^{13}C NMR δ 143.1, 133.7, 133.6, 135.7, 135.7, 129.66, 129.63, 128.2, 127.7, 127.2, 125.6, 81.4, 80.0, 66.3, 34.5, 28.1, 26.9, 19.3.

[2*R*,5*R*,(S)*R*]-2-Methyl-5-[(*p*-tolylsulfinyl)methyl]tetrahydrofuran (30). Compound **30** was obtained from **15** following Method E (eluent EtOAc) as a colorless oil, in 85% yield: $[\alpha]^{20}_D$ +68 (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 7.56 and 7.31 (4H, AA′BB′ system), 3.93 (1H, m), 3.93, 3.19 and 2.86 (3H, ABX system, J = 12.8, 6.2, 5.9 Hz), 2.40 (3H, s), 2.03 (2H, m), 1.85 (1H, m), 1.54 (1H, m), 1.25 (3H, d, J = 6 Hz); ^{13}C NMR δ 141.6, 140.6, 129.9, 124.4, 76.1, 73.8, 63.4, 32.7, 31.1, 21.4, 21.3.

(2*R*,5*R*)-2-Methyl-5-(hydroxymethyl)tetrahydrofuran (31). To a solution of compound **30** (130 mg, 0.55 mmol) and 2,4,6-collidine (219 μL, 1.65 mmol) in CH_3CN (4 mL) was added trifluoroacetic anhydride (389 μL, 2.75 mmol) at 0 °C. After being stirred at 0 °C for 10 min, the mixture was neutralized with a 20% K_2CO_3 solution (3 mL). Then, an excess of $NaBH_4$ (103 mg, 2.75 mmol) was added at 0 °C, and the mixture was stirred for 30 min at rt and quenched with saturated NH_4Cl. The mixture was neutralized with a 20% K_2CO_3 solution and extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. Excess collidine was removed by treatment of a solution of the crude mixture in CH_2Cl_2 with excess zinc chloride. After being stirred for 1 h at rt, the mixture was filtered. After workup and flash chromatography (eluent ethyl ether), compound **31** was obtained as a colorless oil, in 63% yield: $[\alpha]^{20}_D$ −11 (*c* 2, C_2H_5OH); ^{1}H NMR δ 3.99 (1H, m), 3.68 and 3.48 (3H, ABX system, J = 11.5, 3.2 and 5.7 Hz), 2.27 (1H, br s), 2.1−1.3 (4H, m), 1.23 (3H, d, J = 6 Hz); ^{13}C NMR δ 79.5, 76.0, 65.3, 33.2, 27.3, 21.1.

(2*S*,6*R*)-2-(*p*-Methoxyphenyl)-6-(hydroxymethyl)tetrahydropyran (33). To a solution of compound **21** (100 mg, 0.29 mmol) and 2,4,6-collidine (115 μL, 0.87 mmol) in CH_3CN (3 mL) was added trifluoroacetic anhydride (205 μL, 1.45 mmol) at 0 °C. After the solution was stirred at 0 °C for 10 min, water (1 mL) was added and the resulting solution was neutralized with solid K_2CO_3. After an additional 30 min of stirring, an excess of $NaBH_4$ was added. The mixture was stirred for 1 h at rt and quenched at 0 °C with saturated NH_4Cl. The solution was extracted with ethyl acetate and washed with 1 M HCl, saturated $NaHCO_3$, and brine. After workup and flash chromatography (eluent EtOAc/hexane 1:1), compound **33** was obtained as a colorless oil, in 91% yield: $[\alpha]^{20}_D$ −53 (*c* 0.806, $CHCl_3$); ^{1}H NMR δ 7.29 and 6.88 (4H, AA′BB′ system), 4.36 (1H, m), 3.61 (1H, m), 3.80 (3H, s), 2.24 (1H, br s), 2.0−1.2 (6H, m); ^{13}C NMR δ 159.4, 135.7, 127.7, 114.1, 79.9, 79.1, 66.7, 55.7, 33.9, 27.3, 23.9; MS (EI) *m*/*z* 222 (M^+, 49), 191 (97), 147 (100), 135 (68), 121 (57), 109 (20); HRMS (EI) calcd for $C_{13}H_{18}O_3$ (M^+) 222.1256, found 222.1246.

(2*S*,6*R*)-2-(*p*-Methoxyphenyl)-6-formyltetrahydropyran (34). Method A. To a mixture of PCC (400 mg, 1.44 mmol), 4A molecular sieves (1 g/mmol alcohol), and Celite (400 mg) previously dried under vacuum, in CH_2Cl_2 (5 mL), was added a solution of **33** (80 mg, 0.36 mmol) in CH_2Cl_2 (3 mL) at rt. After the mixture was stirred for 3 h at rt, ethyl ether was added, and the resulting mixture was filtered through silica gel, washed with ethyl ether, and concentrated under reduced pressure to give aldehyde **34** as a colorless oil, in 81% yield.

Method B. To a solution of compound **21** (380 mg, 1.10 mmol) and 2,4,6-collidine (440 μL, 3.31 mmol) in CH_3CN (11 mL) was added trifluoroacetic anhydride (780 μL, 5.52 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min and quenched with saturated $NaHCO_3$. After an additonal 3 h of stirring at rt, extraction with EtOAc, workup, and flash chromatography (eluent EtOAc/hexane 2:3), compound **34** was obtained as a colorless oil, in 82% yield: $[\alpha]^{20}_D$ −6 (*c* 0.874, $CHCl_3$); ^{1}H NMR δ 9.71 (1H, s), 7.33 and 6.90 (4H, AA′BB′ system), 4.43 (1H, m), 3.98 (1H, m), 3.81 (3H, s), 2.1−1.3 (6H, m); ^{13}C NMR ($CDCl_3$) 202.7, 159.6,134.8, 127.6, 114.2, 82.6, 80.1, 55.7, 33.5, 26.4, 23.7. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.22; H, 7.32. Found: C, 69.79; H, 7.35.

(*p*-Benzyloxybenzyl)triphenylphosphonium bromide (36). Commercially available *p*-benzyloxy benzyl alcohol (**35**) was transformed into *p*-benzyloxybenzyl bromide following the method previously reported.[27] To a solution of the resulting bromide (1.88 g, 6.8 mmol) in toluene (50 mL) was added PPh_3 (5.34 g, 20.3 mmol) at rt. The reaction mixture was refluxed for 20 h and concentrated under reduced pressure. The residue was dissolved in ethyl ether, and the precipitate was filtered, washed with ethyl ether, and concentrated under reduced pressure to give the phosphonium salt **36** as a white solid, in quantitative yield: mp 235 °C; ^{1}H NMR δ 7.8−7.3 (2H, m), 7.01 and 6.70 (4H, AA′BB′ system), 5.30 (2H, d, J = 13.7 Hz), 4.96 (2H, s); ^{13}C NMR ($CDCl_3$) 158.7, 134.9, 134.4, 134.3, 132.7, 132.7, 130.2, 130.0, 128.5, 128.0, 127.4, 118.5, 117.3, 115.1, 69.9, 44.5; MS (EI) *m*/*z* 459 (M^+ − Br, 100), 262 (10), 183 (8),

91 (65); HRMS (EI) calcd for $C_{32}H_{28}OP$ (M^+ − Br) 459.1878, found 459.1875.

(2*S*,6*R*)-6-[(*p*-Benzyloxyphenyl)vinyl]-2-(*p*-methoxyphenyl)tetrahydropyran (37). To a solution of phosphonium salt **36** (245 mg, 0.45 mmol) in THF (5 mL) at 0 °C was added *n*-BuLi (284 μL of a 1.6 M solution in hexanes, 0.45 mmol). The solution turned orange and was stirred for 15 min at 0 °C. Then, a solution of aldehyde **34** (50 mg, 0.23 mmol) in THF (1 mL) was added. The mixture was stirred at 0 °C for 30 min before addition of silica gel. After being stirred for 15 min at rt, the solution was filtered and concentrated under reduced pressure. After flash chromatography (eluent EtOAc/hexane 1:5), compound **37** was obtained as a white solid, in 96% yield as a 3:2 mixture of *Z*/*E* isomers: ^{1}H NMR δ 7.5−6.8 (13H, m), 6.96 (1H, d, J = 15.9 Hz), 6.51 (1H, d, J = 11.8 Hz), 6.17 (1H, dd, J = 15.9, 5.9 Hz), 5.68 (1H, dd, J = 11.8, 8.6 Hz), 5.09 (2H, s), 5.07 (2H, s), 4.42 (1H, m), 4.41 (1H, m), 4.18 (1H, m), 3.81 (3H, s), 2.1−1.5 (6H, m); ^{13}C NMR δ 159.3, 158.7, 158.4, 137.4, 137.4, 136.0, 135.9, 132.0, 131.2, 130.6, 130.4, 129.6, 129.4, 129.0, 129.0, 128.4, 128.4, 128.0, 127.9, 127.8, 127.7, 115.3, 115.0, 114.1, 80.0, 79.4, 79.3, 75.3, 70.4, 55.7, 33.8, 33.2, 32.2, 32.0, 24.5, 24.3. Anal. Calcd for $C_{27}H_{28}O_3$: C, 80.96; H, 7.05. Found: C, 80.61; H, 7.04.

(2*S*,6*R*)-2-(*p*-Methoxyphenyl)-6-[*β*-(*p*-hydroxyphenyl)-ethyl]tetrahydropyran (1) [(−)-Centrolobine]. A mixture of **37** (150 mg, 0.37 mmol) and Pd/Al_2O_3 (150 mg) in THF was stirred under hydrogen pressure of 50 bar at rt for 4 h. The resulting mixture was filtered, washed with THF, and concentrated under reduced pressure to give pure (−)-centrolobine (**1**) as a white solid, in 93% yield: mp 85 °C (lit.[24] mp 84−86 °C); $[\alpha]^{20}_D$ −93 (*c* 1, $CHCl_3$) [lit.[24] $[\alpha]^{20}_D$ −92.1 (*c* 1, $CHCl_3$)]; ^{1}H NMR δ 7.34 and 6.90 (4H, AA′BB′ system), 7.04 and 6.71 (4H, AA′BB′ system), 5.43 (1H, br s), 4.33 (1H, m), 3.47 (2H, m), 3.81 (3H, s), 2.70 (2H, s), 2.0−1.2 (8H, m); ^{13}C NMR δ 159.1, 154.0, 136.2, 134.8, 129.9, 127.6, 115.6, 114.1, 79.6, 77.7, 66.7, 55.7, 38.7, 33.6, 31.7, 31.2, 24.5. Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.78; H, 7.74. Found: C, 76.50; H, 7.82.

[2*R*,6*R*,(S)*R*]-(6-Methyltetrahydropyran-2-yl)(*p*-tolylsulfinyl)acetic Acid (38). To a solution of **22** (76 mg, 0.30 mmol) in THF (10 mL) was added dropwise MeLi (282 μL of a 1.6 M solution in ether, 0.45 mmol) at −78 °C. After the mixture was stirred for 30 min at −78 °C, a stream of CO_2 was passed through it for 45 min at 0 °C. The reaction was quenched with water, and THF was removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 and then acidified with 1 M HCl to obtain the carboxylic acid which was dissolved in CH_2Cl_2. After workup, compound **38** was obtained as a colorless oil, in 83% yield as a mixture of epimers: ^{1}H NMR δ 7.6−7.1 (8H, m), 6.24 (1H, br s), 6.09 (1H, br s), 3.77 (2H, m), 3.54 (2H, m), 3.24 (2H, m), 2.41 (3H, s), 2.36 (3H, s), 2.0−1.2 (12H, br m), 1.13 (3H, d, J = 6.4 Hz), 1.03 (3H, d, J = 6.4 Hz).

(2*R*,6*R*)-(6-Methyltetrahydropyran-2-yl)acetic Acid ((−)-2). To a stirred solution of **38** (50 mg, 0.17 mmol) in absolute ethanol was added a large excess of activated Raney Ni, and the mixture was vigorously stirred for 1 h at rt. Raney Ni was removed by filtration through a Celite pad and washing with ethanol. Ethanol was removed under reduced pressure, and a K_2CO_3-saturated solution was added. The aqueous layer was extracted with CH_2Cl_2 and then acidified with 1 M HCl to obtain the crude carboxylic which was dissolved in CH_2Cl_2. After workup, compound (−)-**2** was obtained as a colorless oil, in 71% yield: $[\alpha]^{20}_D$ −22 (*c* 1.3, $CHCl_3$) [lit.[31p] $[\alpha]^{20}_D$ −24.8 (*c* 1, $CHCl_3$)]; ^{1}H NMR δ 3.77 (1H, m), 3.54 (1H, m), 2.57 (1H, dd, J = 7.5, 16.1 Hz), 2.50 (1H, dd, J = 16.1, 5.0 Hz), 1.9−1.2 (6H, m), 1.19 (3H, d, J = 6.2 Hz); ^{13}C NMR δ 174.4, 74.6, 73.9, 41.1, 32.7, 30.7, 23.1, 22.0.

[2*S*,6*S*,(S)*R*]-(6-Methyltetrahydropyran-2-yl)(*p*-tolylsulfinyl)acetic Acid (39). Compound **39** was obtained following the procedure reported for **38** as a colorless oil, in 82% yield as a mixture of epimers: ^{1}H NMR δ 8.92 (1H, br s), 7.6−7.2 (4H, br m), 3.99 (1H, m), 3.69 (1H, m), 3.50 (1H, m), 2.39 (3H, s), 2.0−1.3 (6H, m), 1.27 (3H, d, J = 6.3 Hz); ^{13}C NMR δ 166.9, 166.2, 142.8, 142.3, 138.1, 136.1, 130.1, 130.0, 125.5, 124.3, 75.4, 74.8, 73.1, 72.5, 67.8, 32.6, 32.5, 29.4, 28.5, 23.1, 23.0, 21.4, 21.5, 21.7; MS (EI) *m*/*z* 296 (M^+, 4), 236 (11), 157 (19), 139 (64), 124 (60), 99 (40), 84 (100), 69 (42); HRMS (EI) calcd for $C_{15}H_{20}O_4S$ (M^+) 296,1082, found 296,1073.

(2*S*,6*S*)-(6-Methyltetrahydropyran-2-yl)acetic Acid ((+)-2). Compound (+)-**2** was obtained from **39** following the procedure reported for (−)-**2** as a colorless oil, in 75% yield: $[\alpha]^{20}_D$ +26 (*c* 0.18, $CHCl_3$) [lit.[31d] $[\alpha]^{20}_D$ +26 (*c* 0.18, $CHCl_3$)]; ^{1}H NMR δ 6.6 (1H, br s), 3.77 (1H, m), 3.54 (1H, m), 2.56 (1H, m), 2.52 (1H, m), 1.8−1.2 (6H, m), 1.19 (3H, d, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) 174.4, 74.6, 73.9, 41.1, 32.7, 30.7, 23.1, 22.0.

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Supporting Information Available: General experimental paragraph; ^{1}H and ^{13}C NMR spectra for compounds **14**−**18**, **21**−**23**, **25**, **29**−**31**, **1**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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