

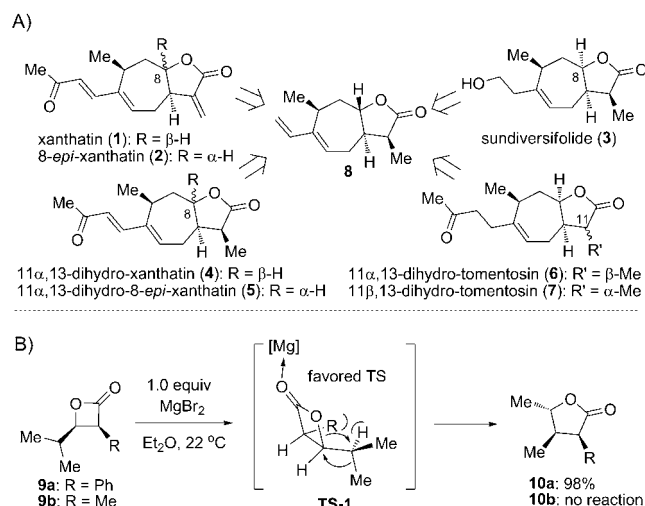
Enantioselective and Collective Syntheses of Xanthanolides Involving a Controllable Dyotropic Rearrangement of *cis*- β -Lactones**

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Dedicated to Professor Manfred T. Reetz

Chemo-, regio-, and stereoselective rearrangements, especially those that lead to skeletal reorganization, are widely appreciated as powerful transformations in organic synthesis.^[1] A typical example is the Wagner–Meerwein-type dyotropic rearrangement of β -lactones,^[2–5] a rearrangement, which involves concurrent migration of two vicinal σ bonds (one C–O bond and one C–C bond) to generate the ring-enlarged product, that is, γ -butyrolactones. Mechanistically, most of the documented dyotropic rearrangements of β -lactones are concerted and the migrating C–C bond and C–O bond are antiperiplanar in the transition state.^[2] Surprisingly, the synthetic utility of this intriguing transformation has been largely overlooked, despite it being a useful method for constructing γ -butyrolactones, which are ubiquitous motifs in biologically active compounds.^[6] The low usage of this transformation may be attributed to unpredictable product distributions, which are sensitive to reaction parameters, such as the identity of substrates and Lewis acids.

To explore the full potential of dyotropic reactions involving β -lactones, we aimed at developing synthetic routes to the xanthanolides (Scheme 1A, **1–7**), a large group of natural products that were isolated primarily from the genus *Xanthium*.^[7] The xanthanolides' wide range of biological activities, which include antitumor, antimicrobial, anti-inflammatory, and allelopathic activities,^[8] have



Scheme 1. A) Naturally occurring xanthanolides and the key synthetic intermediate **8**. B) Wagner–Meerwein-type dyotropic rearrangement of *cis*- β -lactones.

prompted total synthesis studies involving a number of strategies, although most of them suffer from long linear sequences (>15 steps) and low overall yields (less than 10%).^[9] Of particular interest to us is the recently demonstrated trypanocidal activity (IC₅₀ = 10 μ M against blood stream forms of *Trypanosoma brucei brucei*) of xanthatin (**1**).^[10] A de novo synthetic approach that enables efficient exploration of the structure-activity relationships of these natural products, coupled with a genome-wide RNA-interference library screen platform in *T. brucei*,^[11] would provide valuable cues as to the mode of action of these natural products and thus hopefully contribute to combating human African trypanosomiasis, which is a deadly yet therapeutically neglected disease.^[12]

With regard to a synthetic strategy, we envisioned that the highly substituted γ -butyrolactone **8**,^[9b,h] if made in a concise and scalable manner, would allow straightforward access to xanthanolides wherein the γ -butyrolactone is either *cis*- or *trans*-fused to the seven-membered carbocycle. Notably, in the first report on the Wagner–Meerwein-type dyotropic rearrangement, Mulzer and Brüntrup demonstrated the quantitative conversion of *cis*- β -lactone **9a** into γ -butyrolactone **10a**, which possesses the same stereochemistry of **8** (Scheme 1B).^[3a] The presence of conformations containing high-energy *syn*-pentane interactions in the substrate restricts the substrate to a conformation wherein the subsequent

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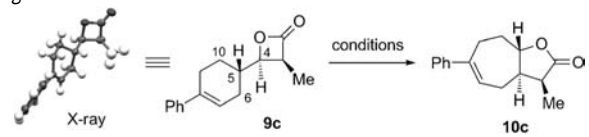
rearrangement involves the migration of only one of the diastereotopic methyl groups (**TS-1**).^[13] However, when we attempted the same rearrangement using *cis*- β -lactone **9b** as the starting material, only **9b** was recovered (Scheme 1B), thus indicating the crucial role of the phenyl group in **9a** in facilitating the rearrangement under the reaction conditions. This result necessitated further investigation of the dyotropic rearrangement of α -methyl-*cis*- β -lactones before it could be used for the preparation of biologically active natural products such as the xanthanolides. Herein we describe our efforts in identifying reaction conditions for expanding the substrate scope of this stereospecific rearrangement; this methodology provided a foundation for the collective total syntheses^[14] of the naturally occurring xanthanolides (**1–7**) as well as their unnatural analogues.

Toward evaluating the aforementioned transformation using a model compound that is relevant to the total synthesis of the xanthanolides, we commenced our studies by synthesizing enantioenriched β -lactone **9c** by employing two organocatalytic reactions, one of which was developed by the research group of MacMillan and the other by the research group of Nelson (see the Supporting Information for details).^[15,16] Satisfyingly, the X-ray crystallographic analysis of **9c** confirmed the antiperiplanar relationship of the C5–C6 σ bond and the C4–O σ bond (see scheme in Table 1).^[17] If the conformation of the transition state structure of the dyotropic reaction of **9c** is similar to the solid-state conformation of **9c**, we anticipate that the migration of the C5–C6 σ bond would be more favored than that of the C5–C10 and C5–H σ bonds, thus affording γ -butyrolactone **10c** as the major product. Encouraged by this rationalization, we screened various Lewis acids that we thought could facilitate the rearrangement; among these, the use of MgBr_2 (Table 1, entry 1), $\text{Zn}(\text{OTf})_2$, $\text{In}(\text{OTf})_3$, $\text{Yb}(\text{OTf})_3$, and TMSOTf failed to promote the desired transformation and led to recovery of the starting material or substantial decomposition. Pleasingly,

γ -butyrolactone **10c** was obtained in 67% yield by using a stoichiometric amount of TiCl_4 , although the product was contaminated by an inseparable unidentified byproduct (Table 1, entry 2). Ultimately, we found that when **9c** was treated with EtAlCl_2 for 5 minutes at room temperature in either CH_2Cl_2 or toluene **10c** was obtained as the predominant product (Table 1, entries 3 and 4). Surprisingly, the reaction was complete within a short period of time and reducing the reaction time to 2 minutes led to **10c** being isolated in 85% yield (Table 1, entry 5). Several other aluminum Lewis acids were examined: whereas Et_2AlCl was as effective in mediating the reaction as EtAlCl_2 (Table 1, entry 6), a sluggish reaction was observed when Et_3Al was used. Specifically, when **9c** was treated with Et_3Al for 3 hours, **10c** was isolated in 42% yield and the substrate **9c** was recovered in 48% yield (Table 1, entry 7). In sharp contrast, the use of AlCl_3 led to complete decomposition of **9c** (Table 1, entry 8), thus indicating that the nature of the organoaluminum Lewis acid is crucial for the rearrangement. When the reaction temperature was reduced to -40°C , the rate of the reaction was lower and hence a reaction time of 4 hours was required to achieve full conversion of **9c** (Table 1, entry 9). The use of a catalytic amount of EtAlCl_2 was also effective, although a longer reaction time was required and **10c** was isolated in lower yield than the reaction wherein a stoichiometric amount of EtAlCl_2 was used (Table 1, entry 10 versus entry 5). To the best of our knowledge, there is no precedent for the organoaluminum-promoted dyotropic rearrangement of β -lactones.^[18] Importantly, compound **10c** was isolated as a single diastereomer, the structure of which was determined unambiguously by X-ray crystallography.^[17]

The scope of the EtAlCl_2 -mediated Wagner–Meerwein-type dyotropic rearrangement was investigated with respect to various *cis*- β -lactones (Table 2). Enantiopure β -lactones **9d–9f** were converted into the corresponding *trans*-fused [5.3.0] bicycles **10d–10f** in good yields (Table 2, entries 1–3); notably, **10f** only differs from **8**, the key intermediate toward the xanthanolides, by the absence of a methyl group. The rearrangement of **9g** also proceeded smoothly to afford tricycle **10g** (Table 2, entry 4). Moreover, [4.3.0] bicyclic compound **10h** was obtained in 82% yield from β -lactone **9h**, suggesting that this protocol has the potential to construct polycyclic systems other than [5.3.0] bicycles (Table 2, entry 5).^[19] The superiority of EtAlCl_2 over MgBr_2 in promoting the current reaction of α -methyl-*cis*- β -lactones was evident again in the successful conversion of **9b** into **10b** in quantitative yield under the optimized conditions (Table 2, entry 6 versus Scheme 1B). In the case of β -lactone **9i**, the phenyl group migrated in the transformation, thus furnishing **10i** in 78% yield (Table 2, entry 7). Most interestingly, a pair of diastereomers, *cis*- β -lactones **9j** and **9k**, underwent methyl migration and 2-phenylethyl migration, respectively, to form the corresponding trisubstituted γ -butyrolactones **10j** and **10k**, respectively (Table 2, entries 8 and 9), thus demonstrating that this reaction is stereospecific. In addition to α -methyl *cis*- β -lactones, a α -ethyl-*cis*- β -lactone, **9l**, also underwent the EtAlCl_2 -mediated rearrangement, thus affording **10l** in 76% yield (Table 2, entry 10).

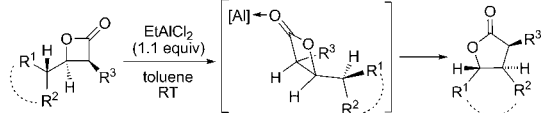
Table 1: Optimization of reaction conditions for the dyotropic rearrangement of **9c** into **10c**.^[a]



Entry	Lewis acid	Solvent/T	t	Yield [%] ^[b]
1	MgBr_2	Et_2O , RT	12 h	0 ^[c]
2	TiCl_4	CH_2Cl_2 , RT	1 h	67 ^[d]
3	EtAlCl_2	CH_2Cl_2 , RT	5 min	73
4	EtAlCl_2	toluene, RT	5 min	75
5	EtAlCl_2	toluene, RT	2 min	85
6	Et_2AlCl	toluene, RT	2 min	81
7	AlEt_3	toluene, RT	3 h	42 ^[e]
8	AlCl_3	toluene, RT	3 h	0 ^[c]
9	EtAlCl_2	toluene, -40°C	4 h	70
10 ^[f]	EtAlCl_2	toluene, RT	1.5 h	67

[a] [**9c**] = 0.025 M (0.3 mmol), 1.1 equiv Lewis acid. [b] Yields after column chromatography. [c] Substrate **9c** decomposed. [d] Yield determined by NMR analysis using mesitylene as internal standard. [e] Substrate **9c** was recovered in 48% yield. [f] 0.2 equiv Lewis acid was used.

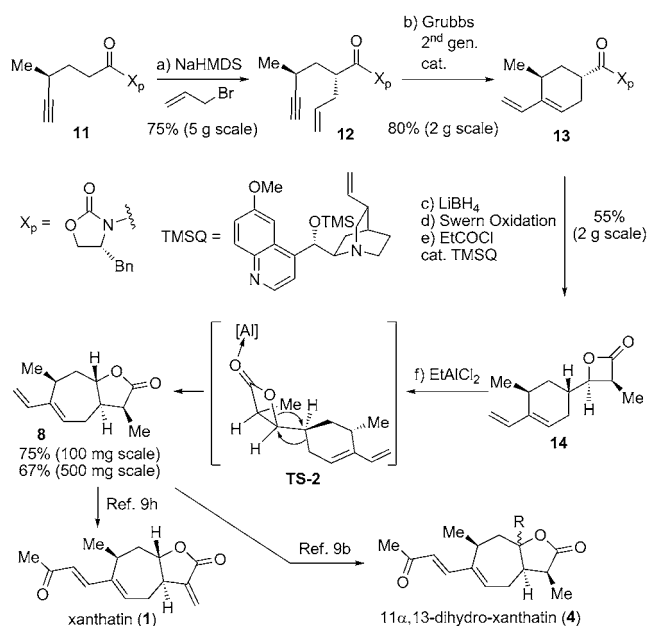
Table 2: Scope of the EtAlCl₂-mediated Wagner–Meerwein-type dyotropic rearrangement of *cis*-β-lactones.^[a]



Entry	β-lactones	Product	Yield [%] ^[b]
1			83
2			88
3			77
4			71
5			82
6			99
7			78
8			76
9			82
10			76

[a] Conditions: β-lactone (0.3 mmol, 0.025 M), EtAlCl₂ (1.1 equiv), toluene, RT, 2 min. Note: β-lactones and rearrangement products were isolated in > 19:1 diastereomeric ratio.

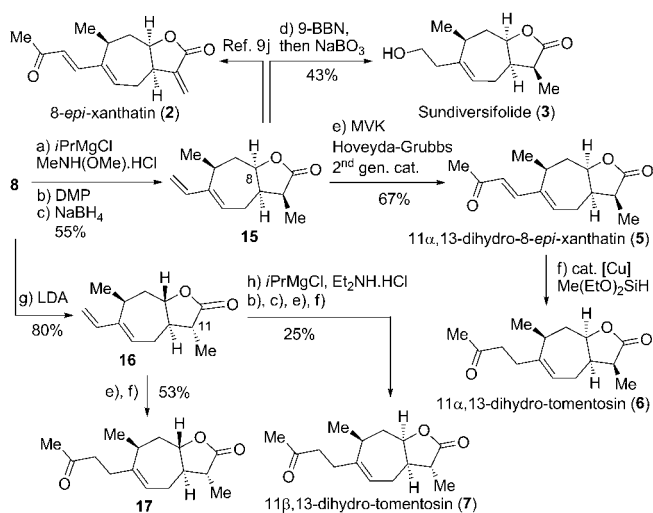
After establishing this synthetic methodology, we then moved toward the total syntheses of various xanthane-type sesquiterpenoids involving intermediate **8** (Scheme 2). Diastereoselective allylation of compound **11**^[20] afforded **12** (75% yield, 5 g scale), which was then subjected to ring-closing enyne metathesis to give compound **13** (80% yield, 2 g scale). Consecutive reduction and oxidation yielded the aldehyde, which was then subjected to an organocatalytic asymmetric [2+2] reaction with propionyl chloride to give *cis*-β-lactone **14** as a single diastereomer in 55% yield over three steps (2 g scale). The desired compound **8** was then obtained



Scheme 2. Synthesis of the key intermediate **8**. Reagents and conditions: a) NaHMDS (1.1 equiv), THF, −78 °C; then allyl bromide (3.0 equiv), −40 °C; b) Grubbs 2nd generation cat. (10 mol %), ethylene, toluene, 40 °C; c) LiBH₄ (1.0 equiv), MeOH (1.0 equiv), THF, 0 °C; d) (COCl)₂ (2.0 equiv), DMSO (4.0 equiv), Et₃N (8.0 equiv), CH₂Cl₂, −78 °C to 0 °C; e) TMSQ (10 mol %), LiClO₄ (3.0 equiv), DIPEA (2.5 equiv), EtCOCl (2.0 equiv), Et₂O/CH₂Cl₂ (1:2), −40 °C; f) EtAlCl₂ (1.1 equiv), toluene, RT. DIPEA = diisopropylethylamine, DMSO = dimethylsulfoxide, NaHMDS = sodium hexamethyldisilazide, TMS = trimethylsilyl.

by the EtAlCl₂-mediated dyotropic rearrangement, although the yield upon isolation fell from 75% to 67% when the reaction was scaled up from 100 mg to 500 mg. The high chemo-, regio- and stereoselectivity of this key transformation can be rationalized by considering the transition state **TS-2** (Scheme 2). The analytical data of **8** were identical to those reported for the compound previously; in these previous reports, **8** was converted to natural products xanthatin (**1**) and 11α,13-dihydroxanthatin (**4**) in three steps and two steps, respectively.^[9b,h]

With a scalable method for the preparation of the critical intermediate **8** established, we proceeded to make a variety of xanthanolides wherein the γ-butyrolactone moiety is *cis* fused to the seven-membered carbocycle (Scheme 3). Ring-opening of γ-butyrolactone **8** with *N,O*-dimethylhydroxylamine hydrochloride followed by redox manipulations and lactonization effected the inversion of the C8 stereogenic center, thus affording bicycle **15** in 55% yield over three steps. Notably, compound **15** was synthesized en route to (+)-8-*epi*-xanthatin (**2**) by Shindo and co-workers.^[9j] Hydroboration of **15** and subsequent oxidation gave sundiversifolide (**3**). Cross metathesis of compound **15** and methyl vinyl ketone (MVK) catalyzed by the second-generation Hoveyda–Grubbs catalyst furnished 11α,13-dihydro-8-*epi*-xanthatin (**5**), which was further converted into 11α,13-dihydro-tomentosin (**6**) through a copper-catalyzed 1,4-reduction.^[21] On the other hand, the C11 stereogenic center in **8** could be readily inverted by



Scheme 3. Syntheses of various xanthane sesquiterpenoids from **8**. Reagents and conditions: a) *i*PrMgCl (5.0 equiv), MeNH(OMe)·HCl (2.5 equiv), THF, 0°C; b) DMP (1.2 equiv), CH₂Cl₂, RT; c) NaBH₄ (2.5 equiv), MeOH, 0°C; d) 9-BBN (5.0 equiv), THF, reflux, then NaBO₃, RT; e) MVK (20.0 equiv), Hoveyda–Grubbs 2nd generation cat. (10 mol%), CH₂Cl₂, 40°C; f) Cu(OAc)₂ (0.5 equiv), P(O*i*Pr)₃ (1.0 equiv), Me(EtO)₂SiH (1.5 equiv), toluene, RT; g) LDA (5.0 equiv), THF, 0°C; h) *i*PrMgCl (5.0 equiv), Et₂NH·HCl (2.5 equiv), THF, 0°C. DMP = Dess–Martin periodinane, LDA = lithium diisopropylamine, 9-BBN = 9-borabicyclo[3.3.1]nonane.

treatment with LDA, thus giving **16**, which was transformed into 11β,13-dihydro-tomentosin (**7**) through a reaction sequence similar to that used in the synthesis of **6**. By performing cross metathesis of **16** and MVK followed by 1,4-reduction, we were also able to access **17**, a diastereoisomer of **7**. Notably, the structure of an isolated natural product was reassigned from **17** to **7** based on NMR spectral analysis;^[22] we were able to support this reassignment by comparing the spectra of our synthesized compounds with those of the isolated natural product. The ¹H NMR and ¹³C NMR spectra of the synthesized sesquiterpenoids **3**, **5**, and **6** are identical to those of the isolated compounds.

In summary, we have developed a general method, which involves a controllable Wagner–Meerwein-type dyotropic rearrangement of *cis*-β-lactones, for the synthesis of enantiopure trisubstituted γ-butyrolactones. This method should find wide application in synthesis. Herein, we applied this method in an efficient preparation of a number of xanthanolide natural products. Another potentially promising application is the conversion of α-methyl-γ-butyrolactones into α-methylene-γ-butyrolactones, a moiety that has proven vital for the biological activities of many natural products.^[6] The compounds prepared in our studies will be screened for biological activity. The screening of diastereomers will enable us to explore stereochemistry-based structure–activity relationships, which can be extremely informative.^[23] These investigations are underway and will be reported in due course.

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- [1] For a selection of leading reviews on some representative rearrangements, see: a) T. Nakai, K. Mikami, *Chem. Rev.* **1986**, *86*, 885–902; b) K. Prantz, J. Mulzer, *Chem. Rev.* **2010**, *110*, 3741–3766; c) A. M. Martín Castro, *Chem. Rev.* **2004**, *104*, 2939–3002; d) Z.-L. Song, C.-A. Fan, Y.-Q. Tu, *Chem. Rev.* **2011**, *111*, 7523–7556.
- [2] I. Fernández, F. P. Cossío, M. A. Sierra, *Chem. Rev.* **2009**, *109*, 6687–6711.
- [3] a) J. Mulzer, G. Brüntrup, *Angew. Chem.* **1979**, *91*, 840–841; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 793–794; b) J. Mulzer, K. Hoyer, A. Müller-Fahrnow, *Angew. Chem.* **1997**, *109*, 1546–1548; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1476–1478.
- [4] a) T. H. Black, J. D. Fields, *Synth. Commun.* **1988**, *18*, 125–130; b) T. H. Black, J. A. Hall, R. G. Sheu, *J. Org. Chem.* **1988**, *53*, 2371–2374; c) T. H. Black, W. J. DuBay, *Tetrahedron Lett.* **1988**, *29*, 1747–1750; d) T. H. Black, W. J. DuBay, P. S. Tully, *J. Org. Chem.* **1988**, *53*, 5922–5927; e) T. H. Black, T. S. McDermott, S. A. Eisenbeis, *Tetrahedron Lett.* **1990**, *31*, 6617–6620.
- [5] a) V. C. Purohit, A. S. Matla, D. Romo, *J. Am. Chem. Soc.* **2008**, *130*, 10478–10479; b) R. L. Davis, C. A. Leverett, D. Romo, D. J. Tantillo, *J. Org. Chem.* **2011**, *76*, 7167–7174.
- [6] a) H. M. R. Hoffmann, J. Rabe, *Angew. Chem.* **1985**, *97*, 96–112; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 94–110; b) R. R. A. Kitson, A. Millemaggi, R. J. K. Taylor, *Angew. Chem.* **2009**, *121*, 9590–9615; *Angew. Chem. Int. Ed.* **2009**, *48*, 9426–9451.
- [7] For a recent review, see: A. Vasas, J. Hohmann, *Nat. Prod. Rep.* **2011**, *28*, 824–842.
- [8] a) Y. S. Kim, J. S. Kim, S.-H. Park, S.-U. Choi, C. O. Lee, S.-K. Kim, Y.-K. Kim, S. H. Kim, S. Y. Ryu, *Planta Med.* **2003**, *69*, 375–377; b) M. Lavault, A. Landreau, G. Larcher, J.-P. Bouchara, F. Pagniez, P. Le Pape, P. Richomme, *Fitoterapia* **2005**, *76*, 363–366; c) I.-T. Kim, Y.-M. Park, J.-H. Won, H.-J. Jung, H.-J. Park, J.-W. Choi, K.-T. Lee, *Biol. Pharm. Bull.* **2005**, *28*, 94–100; d) S. Ohno, K. Tomita-Yokotani, S. Kosemura, M. Node, T. Suzuki, M. Amano, K. Yasui, T. Goto, S. Yamamura, K. Hasegawa, *Phytochemistry* **2001**, *56*, 577–581.
- [9] For an excellent review on this topic, see: a) K. Shishido, *Heterocycles* **2009**, *78*, 873–889. For synthetic efforts, see: b) M. A. Evans, J. P. Morken, *Org. Lett.* **2005**, *7*, 3371–3373; c) D. A. Kummer, J. B. Brenneeman, S. F. Martin, *Org. Lett.* **2005**, *7*, 4621–4623; d) D. A. Kummer, J. B. Brenneeman, S. F. Martin, *Tetrahedron* **2006**, *62*, 11437–11449; e) H. Yokoe, H. Sasaki, T. Yoshimura, M. Shindo, M. Yoshida, K. Shishido, *Org. Lett.* **2007**, *9*, 969–971; f) T. Hashimoto, T. Tashiro, M. Sasaki, H. Takikawa, *Biosci. Biotechnol. Biochem.* **2007**, *71*, 2046–2051; g) K. Ohtsuki, K. Matsuo, T. Yoshikawa, C. Moriya, K. Tomita-Yokotani, K. Shishido, M. Shindo, *Org. Lett.* **2008**, *10*, 1247–1250; h) H. Yokoe, M. Yoshida, K. Shishido, *Tetrahedron Lett.* **2008**, *49*, 3504–3506; i) K. Matsuo, H. Yokoe, K. Shishido, M. Shindo, *Tetrahedron Lett.* **2008**, *49*, 4279–4281; j) K. Matsuo, K. Ohtsuki, T. Yoshikawa, K. Shishido, K. Yokotani-Tomita, M. Shindo, *Tetrahedron* **2010**, *66*, 8407–8419.
- [10] E. Nibret, M. Youns, R. L. Krauth-Siegel, M. Wink, *Phytother. Res.* **2011**, *25*, 1883–1890.
- [11] S. Alsford, S. Eckert, N. Baker, L. Glover, A. Sanchez-Flores, K. F. Leung, D. J. Turner, M. C. Field, M. Berriman, D. Horn, *Nature* **2012**, *482*, 232–236.
- [12] R. Brun, J. Blum, F. Chappuis, C. Burri, *Lancet* **2010**, *375*, 148–159.
- [13] For a similar transition state formulated for the Wagner–Meerwein type dyotropic rearrangement of α-disubstituted β-lactones, see Refs. [4d] and [4e].

- [14] a) P. S. Baran, T. J. Malmone, J. M. Richter, *Nature* **2007**, *446*, 404–408; b) S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* **2011**, *475*, 183–188; c) S. A. Snyder, A. Gollner, M. I. Chiriac, *Nature* **2011**, *474*, 461–466.
- [15] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
- [16] C. Zhu, X. Shen, S. G. Nelson, *J. Am. Chem. Soc.* **2004**, *126*, 5352–5353.
- [17] CCDC 873590 (**9c**), 873591 (**10c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [18] AlBr₃ has been employed in the dyotropic reaction: J. Mulzer, A. Pointner, R. Straßer, K. Hoyer, U. Nagel, *Tetrahedron Lett.* **1995**, *36*, 3679–3682.
- [19] For the use of a Wagner–Meerwein type dyotropic rearrangement for the synthesis of [4.3.0] bicyclic γ -butyrolactones, see Refs. [4c] and [4d].
- [20] The enantiomer of compound **11** has been reported: D. A. Evans, D. H. B. Ripin, D. P. Halstead, K. R. Campos, *J. Am. Chem. Soc.* **1999**, *121*, 6816–6826.
- [21] A. Pešs, E. T. T. Kumpulainen, A. M. P. Koskinen, *J. Org. Chem.* **2009**, *74*, 7598–7601.
- [22] a) J. Jakupovic, C. Zdero, M. Grenz, F. Tschritzis, L. Lehmann, S. M. Hashemi-Nejad, F. Bohlmann, *Phytochemistry* **1989**, *28*, 1119–1131; b) R. Lanzetta, G. Lama, G. Mauriello, M. Parrilli, R. Racioppi, G. Sodano, *Phytochemistry* **1991**, *30*, 1121–1124.
- [23] L. A. Marcaurelle, E. Comer, S. Dandapani, J. R. Duvall, B. Gerard, S. Kesavan, M. D. Lee, H. Liu, J. T. Lowe, J. C. Marie, C. A. Mulrooney, B. A. Pandya, A. Rowley, T. D. Ryba, B. C. Suh, J. Wei, D. W. Young, L. B. Akella, N. T. Ross, Y. L. Zhang, D. M. Fass, S. A. Reis, W. N. Zhao, S. J. Haggarty, M. Palmer, M. A. Foley, *J. Am. Chem. Soc.* **2010**, *132*, 16962–16976.