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Dyotropic Rearrangements of Fused Tricyclic β-Lactones: Application to the Synthesis of (−)-Curcumanolide A and (−)-Curcumalactone

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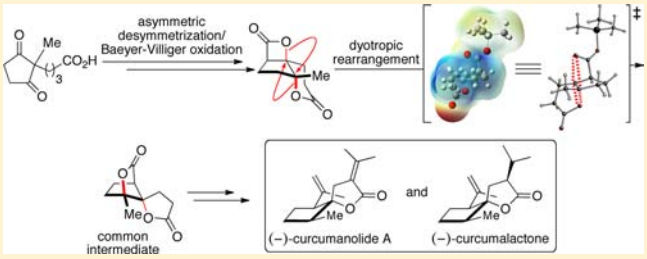
Supporting Information

ABSTRACT: Dyotropic rearrangements of fused, tricyclic β-lactones are described that proceed via unprecedented stereospecific, 1,2-acyl migrations delivering bridged, spiro-γ-butyrolactones. A unique example of this dyotropic process involves a fused bis-lactone possessing both β- and δ-lactone moieties which enabled rapid access to the core structures of curcumanolide A and curcumalactone. Our current mechanistic understanding of the latter dyotropic process, based on computational studies, is also described. Other key transformations in the described divergent syntheses of (−)-curcumanolide A and (−)-curcumalactone from a common intermediate (11 and 12 steps from 2-methyl-1,3-cyclopentanedione, respectively), include a catalytic, asymmetric nucleophile (Lewis base)-catalyzed aldol-lactonization (NCAL) leading to a tricyclic β-lactone, a Baeyer−Villiger oxidation in the presence of a β-lactone, and highly facial-selective and stereocomplementary reductions of an intermediate spirocyclic enoate. The described dyotropic rearrangements significantly alter the topology of the starting tricyclic β-lactone, providing access to complex spirocyclic cyclopentyl-γ-lactones and bis-γ-lactones in a single synthetic operation.



INTRODUCTION

Curcumanolides A (**1**) and B (**2**) are sesquiterpenoid natural products previously isolated from *Curcuma zedoara* and related species (Figure 1).[1] Both of these spirolactones are present in the crude drug Zedoary, the ground rhizome of *C. zedoaria* Roscoe, which has been used medicinally in China for a variety of indications.[2] Curcumalactone (**3**), a dihydro derivative of curcumanolide A, was isolated from *C. aromatica* Silisb[3] and *C. wenyujin*[4] which have long been used as a remedies for cervical cancer in China[5] and were reported to exhibit anti-inflammatory activity.[3] While no information regarding the biological activity of curcumanolides A and B is available, the structural similarity with curcumalactone elevates their interest as targets for further biological studies. In particular, the enoate and spirocylic γ-lactone moieties attracted our interest since these constitute potential electrophilic sites, which could render these natural products as covalent modifiers of their putative cellular targets.

In addition to their potential bioactivity, the unique, functionalized cyclopentane bearing a spirolactone found in these natural products has attracted significant interest from the synthetic community, leading to diverse strategies to access this common core. The first total synthesis of curcumanolide A and the only reported synthesis of curcumalactone to date, both in racemic form, were accomplished by Kato employing a bromonium-induced cyclization/ring contraction route from geraniol.[6] Subsequently, Honda reported the first enantioselective synthesis of curcumanolide A from (−)-carvone establishing the absolute configuration,[7] and Fujita utilized an enzymatic transesterification process to access (−)-curcumanolide A.[8] However, the reported syntheses have led to little additional biological information, and there is no information regarding possible cellular targets.

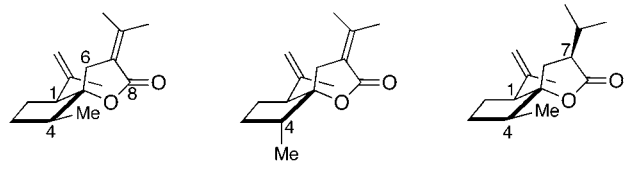


Figure 1. Spirolactone natural products isolated from extracts of *Curcuma* species.

Dyotropic rearrangements were originally defined as reactions in which "two σ-bonds simultaneously migrate intramolecularly" (Figure 2a),[9] but a variety of examples have since been reported in which the simultaneity of the two σ-bond migrations varies from synchronous (and concerted) to asynchronous (and concerted) to stepwise (separated by a discrete intermediate).[10] Several types of dyotropic rearrangements have been employed in various synthetic contexts,

Received: April 17, 2012
Published: August 1, 2012

   dx.doi.org/10.1021/ja303414a | J. Am. Chem. Soc. 2012, 134, 13348−13356

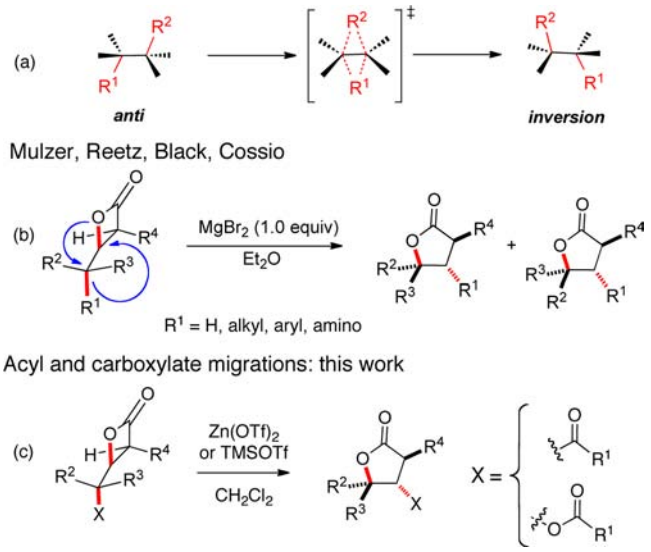


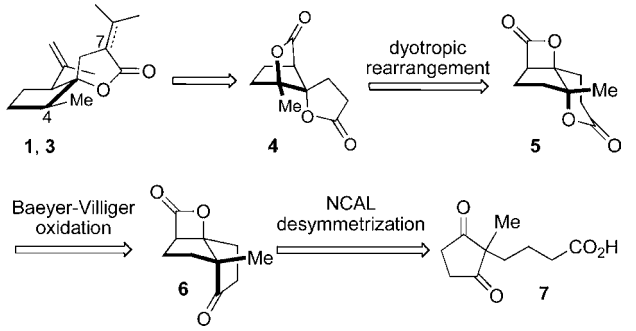
Figure 2. (a) Prototypical dyotropic rearrangement wherein two σ-bonds simultaneously migrate intramolecularly (b) Dyotropic rearrangements of β-lactones involving hydrogen, electron-rich groups, and amino migrations. (c) β-Lactone dyotropic rearrangements involving acyl and carboxylate migrations.

ranging from the early report of a dyotropic interchange of vicinal Br atoms on a steroid skeleton,[11] to more recent applications in the synthesis of *N-cis*-propenyl amides,[12] trisubstituted olefins,[13] and tetraazanaphthalenes.[14] A widely studied dyotropic process, of particular interest to us, is the Lewis acid-mediated rearrangement of β-lactones leading to various γ-butyrolactones (Figure 2b). This area of dyotropic rearrangement chemistry commenced with seminal reports by Mulzer on the ring expansion of β-lactones through a dyotropic process in which the β-lactone oxygen and electron-rich migrating groups exchanged positions.[15] Related reports include Reetz's demonstration that acyclic amino migrating groups allow for the generation of 3-amino-γ-lactones,[16] Cossío's study of the dyotropic rearrangement of propiolactones to γ-butyrolactones under similar conditions,[17] and Black's examination of the dyotropic rearrangement of spirobicyclic β-lactones to a variety of fused γ-butyrolactone systems.[18]

While β-lactone dyotropic reactions with electron-rich migrating groups have been studied extensively, we recently reported the first example of a 1,2-acyl migration in a β-lactone dyotropic process (Figure 2c).[19] This Lewis-acid mediated, stereospecific, dyotropic rearrangement of fused tricyclic β-lactones enables the synthesis of spirocyclic, bridged γ-butyrolactones. Subsequent studies revealed plausible mechanistic pathways for this rearrangement, formulated on the basis of both experimental and theoretical results.[20] We projected that a related dyotropic process involving a bis-lactone bearing both a δ- and a β-lactone moiety would enable efficient access to the spirocyclic core structure of members of the *Curcuma* family of natural products. Herein, we describe concise synthetic routes to (−)-curcumanolide A (**1**) and (−)-curcumalactone (**3**) that demonstrate the utility of these dyotropic processes for complex natural product synthesis with the latter being the first reported asymmetric synthesis.

Retrosynthetic Analysis of Curcumanolides and Curcumalactone. Access to the spirocyclic cores (e.g., **4**, Scheme 1) of the curcumanolides (**1**, **2**) and curcumalactone

Scheme 1. Retrosynthetic Analysis of Curcumalactone and Curcumanolide A

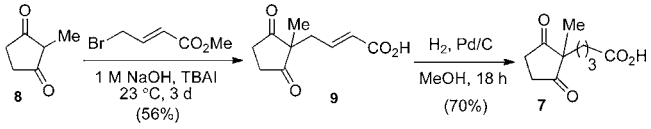


(**3**) was envisioned employing our recently described nucleophile-catalyzed aldol-lactonization (NCAL) process involving desymmetrization of dione **7** with homobenzotetramisole (HBTM) as the Lewis base promoter.[21] This process would deliver tricyclic β-lactone **6** and subsequent Baeyer−Villiger oxidation and dyotropic rearrangement would provide bis-lactone **4** bearing the common spirocyclic core of the targeted natural products. Completion of the synthesis of (−)-curcumalactone and (−)-curcumanolide A would require further transformations of the tricycle **4** including two stereochemistry setting steps that would be dictated by the topologically rich spirocyclic core. In particular, a facially selective hydrogenation of an intermediate cyclopentene would set the C4-methyl-bearing stereocenter of the two targets and a diastereoselective reduction of an enoate would introduce the C7-isopropyl-bearing stereocenter of curcumalactone.

RESULTS AND DISCUSSION

The synthesis of the core structure of both curcumanolide A (**1**) and (−)-curcumalactone (**3**) began with the multigram-scale synthesis of dione acid **7** from commercially available 2-methyl-1,3-cyclopentanedione **8** (Scheme 2). We previously

Scheme 2. Multigram Synthesis of Dione Ketoacid 7 from 1,3-Cyclopentanedione[a]



[a]TBAI, tetrabutylammonium iodide.

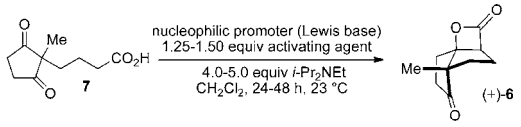
utilized a four-step sequence to access this substrate;[19] however, scale-up of this sequence proved problematic and inefficient. After extensive optimization, a streamlined synthesis of this key substrate was developed involving a one-pot alkylation/hydrolysis sequence to directly deliver dione acid **9** employing commercially available methyl 4-bromocrotonate in 1 M NaOH as solvent under phase transfer conditions. This method enabled production of >20 g of dione acid **9** in a single run and is useful for the large-scale synthesis of a number of related dione acids following hydrogenation of the alkene.[22]

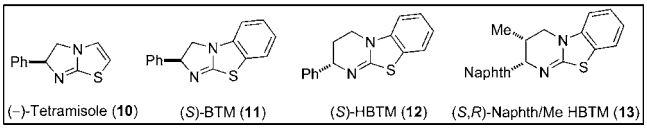
With a scaleable route to dione **7** in hand, extensive optimization was required to develop a practical, catalytic, asymmetric NCAL process to access tricyclic β-lactone (+)-**6**. Initial studies of this transformation employed 1.5 equiv of (−)-tetramisole·HCl (**10**)[23] as a promoter in this desymmet-

dx.doi.org/10.1021/ja303414a | J. Am. Chem. Soc. 2012, 134, 13348−13356

rization process and the modified Mukaiyama reagent **14**, which led to the desired product with high optical purity but only in moderate yields (Table 1, entry 1). Several other carboxylic acid activating agents were explored but led to inferior yields and generally significantly decreased enantioselectivities, especially when catalytic amounts of (−)-tetramisole·HCl were employed (Table 1, entries 2−5). We next studied the use of alternative chiral isothiourea catalysts (**11**−**13**, Table 1) developed by Birman and related to tetramisole (**10**), as Lewis base promoters for the NCAL process.[24] The use of 20 mol % (*S*)-HBTM (**11**)[24a] provided good yields and excellent enantioselectivities (58%, 96% ee) of tricyclic *β*-lactone (+)-**6** in conjunction with *p*-toluenesulfonyl chloride (*p*-TsCl) as activating agent. A further significant increase in yield was realized with use of the mild Lewis acid, LiCl (1.0 equiv), with no sacrifice in enantioselectivity (77%, 96% ee), and this process was utilized to access a number of bicyclic and tricyclic *β*-lactones with good to excellent yields and enantioselectivities.[21]

Table 1. Optimization of the NCAL Process with Dione Acid 7 Leading to Tricyclic *β*-Lactone (+)-6



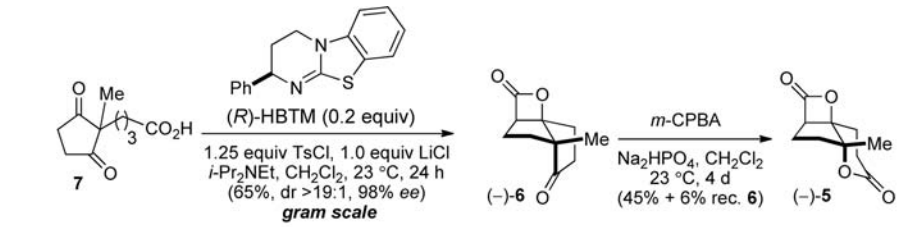


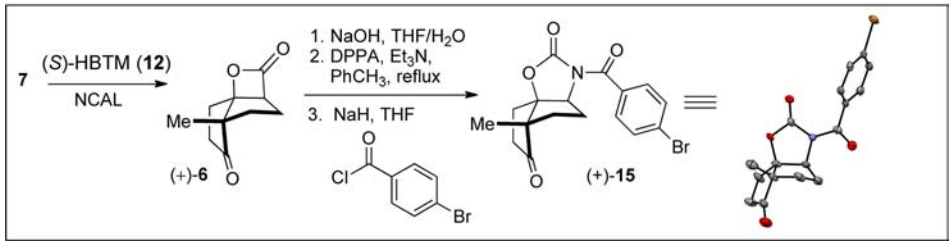
entry	activating agent	Lewis base	% yield[a,b]	% ee[c]
1		(−)-Tet·HCl (**10**, 150 mol%)	35	98[d]
2	*p*-$NO_2C_6H_4SO_2Cl$	(−)-Tet·HCl (**10**, 25 mol%)	11	67[d]
3	CDI	”	34	1.8[d]
4	3,5-$(NO_2)_2$BzCl	”	25	ND
5	*p*-TsCl	”	23	53[d]
6	*p*-TsCl	(*S*)-BTM (**11**, 20 mol%)	33	20[d]
7	*p*-TsCl	(*S*)-HBTM (**12**, 20 mol%)	58 77[e]	96 96[e]
8	**14**	(*S*, *R*)-Naphth/Me HBTM (**13**, 20 mol%)	40	91

[a]Single diastereomer observed by ^{1}H NMR. [b]Refers to isolated, purified products. [c]Determined by chiral GC analysis. [d](−)-Tetramisole·HCl (**10**) and (*S*)-BTM (**11**) provide (−)-**6**. [e]With 1.0 equiv LiCl added. CDI, carbonyldiimidazole; Ts, tosyl; Bz, benzoyl; Napth, naphthyl.

Dyotropic Rearrangements of Tricyclic Acyl-*β*-lactones and Bis-lactones. We began our studies of the dyotropic rearrangement of acyl-*β*-lactones with tricyclic *β*-lactone **16a** (Table 2), available by the NCAL reaction of a cyclohexanedione precursor. We surmised that Lewis acid activation of the *β*-lactone would promote a dyotropic rearrangement via 1,2-acyl migration leading to simultaneous and stereospecific ring expansion of the *β*-lactone to a *γ*-lactone

Scheme 3. Gram-Scale Synthesis of Optically Active Bis-lactone (−)-6 and Confirmation of Absolute Stereochemistry[a,25]

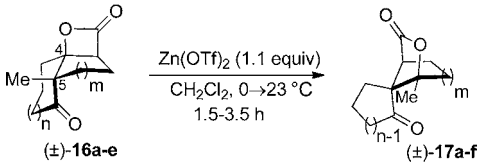


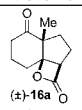
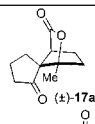
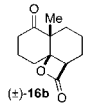
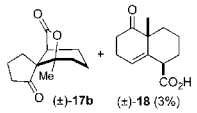
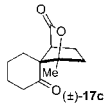
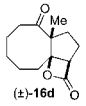
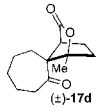
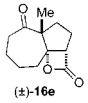
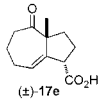
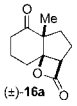
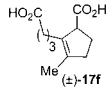


[a]HBTM, homobenzotetramisole; TsCl, *p*-toluenesulfonyl chloride; *m*-CPBA, *m*-chloroperoxybenzoic acid; NCAL, nucleophile-catalyzed aldol lactonization; DPPA, diphenylphosphoryl azide. Inset: ORTEP representation of the X-ray crystal structure of tricyclic carbamate (+)-**15**; hydrogens removed for clarity; thermal ellipsoids shown at 50% probability.

dx.doi.org/10.1021/ja303414a | J. Am. Chem. Soc. 2012, 134, 13348−13356

Table 2. Dyotropic 1,2-Acyl Migration of Tricyclic β-Lactones



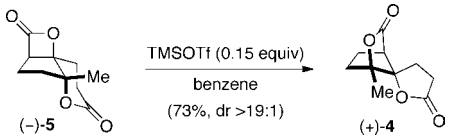
entry	tricyclic-β-lactone	spirocycle	% yield 17[a]
1	 (±)-16a	 (±)-17a	94
2	 (±)-16b	 (±)-17b (±)-18 (3%)	90
3	 (±)-16c	 (±)-17c	85
4	 (±)-16d	 (±)-17d	63
5	 (±)-16e	 (±)-17e	55
6	 (±)-16a	 (±)-17f	73[b]

[a]Refers to isolated yields. [b]Reaction performed using 0.2 equiv TMSOTf at 23 °C for 12 h instead of $Zn(OTf)_2$. Isolated yield of diacid **17f** accompanied by only trace amounts of dyotropic product.

with concomitant ring contraction of the cyclohexanone. It should be noted that in these rigid tricyclic systems, stereospecificity is enforced due not solely to synchronicity of migration but also to ring constraints. Importantly, β-lactone substrate **16** possesses the required antiperiplanar relationship between the migrating C_4-O_1 bond of the β-lactone and the $C_5-C{=}O$ bond of the cyclohexanone. After screening a variety of Lewis acids, including $AlBr_3$, Et_2AlCl, $LaCl_3$, $PrCl_3$, YCl_3, $MgBr_2$, $Yb(OTf)_3$, $In(OTf)_3$, and $Mg(OTf)_2$, the best yields for this transformation were realized using Zn(II) salts, providing up to 94% yield of **17a** when employing 1.1 equiv of $Zn(OTf)_2$ (Table 2, entry 1). Substoichiometric amounts of $Zn(OTf)_2$ led to significant amounts of recovered starting material. Other tricyclic β-lactones **16b–d** were also studied under these conditions and gave excellent yields of bridged γ-lactones **17b–d** (Table 2, entries 2–4) with high stereospecificity (dr >19:1). It is important to note that in the case of tricyclic β-lactone **16e** (entry 5), which lacks the antiperiplanar relationship between the β-lactone C_4-O bond and the C_5-acyl carbon, only olefin acid **17e** was isolated (55%), likely generated from β-lactone opening and subsequent elimination. By a presumed similar pathway, the tricyclic β-lactone **16b** produced trace amounts (3%) of β,γ-unsaturated acid **18** in addition to the expected dyotropic product **17b** in high yield. These two examples provided our initial evidence for carbocation formation in the Zn(II)-promoted dyotropic rearrangement, which was later supported computationally, as detailed below. Interestingly, while Zn(II) salts led to good yields of dyotropic products in most cases, subjecting β-lactone **16a** to catalytic TMSOTf provided only ring-opened diacid **17f** (73%, entry 6), suggestive of an intervening Grob-type fragmentation, which was subsequently confirmed to occur due to adventitious TfOH and not TMSOTf under these conditions.[20] The first dyotropic rearrangement of an optically active tricyclic β-lactone was also performed with lactone (−)-**16a** (97% ee) using $Zn(OTf)_2$ and this provided γ-lactone (−)-**17a** in excellent yield (91%) with high stereochemical fidelity (99% ee, chiral GC).

Toward application of the dyotropic process to the targeted natural products, we studied the rearrangement of tricyclic bis-lactone (−)-**5** bearing both a δ- and β-lactone (Scheme 4).

Scheme 4. Enantioselective Synthesis of Spirolactone (+)-4 via a Bis-lactone Dyotropic Rearrangement[a]



[a]TMSOTf, trimethylsilyl trifluoromethanesulfonate.

While use of $Zn(OTf)_2$ gave only recovered bis-lactone (−)-**5**, a brief survey of Lewis acids led to use of substoichiometric TMSOTf (15 mol %), which slowly produced the desired spiro-γ-lactone (+)-**4** in good yield (73%) and with complete stereochemical fidelity (98% ee).

Mechanistic Studies of the Dyotropic Rearrangement of Tricyclic β-Lactones Involving 1,2-Acyl Migrations. The described dyotropic rearrangements of β-lactones involving 1,2-acyl migrations were unprecedented in type I dyotropic processes.[10a] Our initial hypotheses for this rearrangement invoked a 2-electron-3-centered acylium intermediate or a carboxylate-stabilized, four-membered transition state. Both pathways would benefit from a homoconjugated, carbonyl-assisted migration. However, subsequent theoretical (B3LYP/6-31+G(d,p)) and experimental studies of this dyotropic process (e.g., **16** → **17**, Table 2) revealed that the concertedness of this rearrangement was dependent on the nature of the Lewis acid employed.[20] Theoretical calculations on both the $Zn(OTf)_2$- and $ZnCl_2$-promoted rearrangements of **16a** to **17a** revealed that these reactions occur in a stepwise manner, involving an intermediate with a Zn(II)-complexed carboxylate and a tertiary carbocation center (cf. **19**, Figure 3). However, attempts to trap this carbocation intermediate by both inter- and intramolecular nucleophiles were unsuccessful. These observations are consistent with the computational results, which suggested that the 1,2-acyl shift/carbocation capture process is extremely facile for [6-5] bicyclic

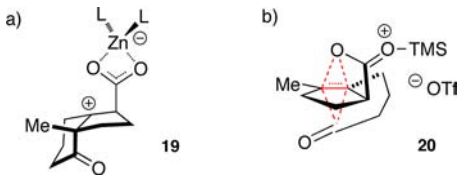


Figure 3. (a) Intermediate for Zn(II)-based Lewis acid-mediated and (b) transition state structure for TMSOTf-mediated, dyotropic rearrangement of tricyclic β-lactone **16a**.

dx.doi.org/10.1021/ja303414a | J. Am. Chem. Soc. 2012, 134, 13348–13356

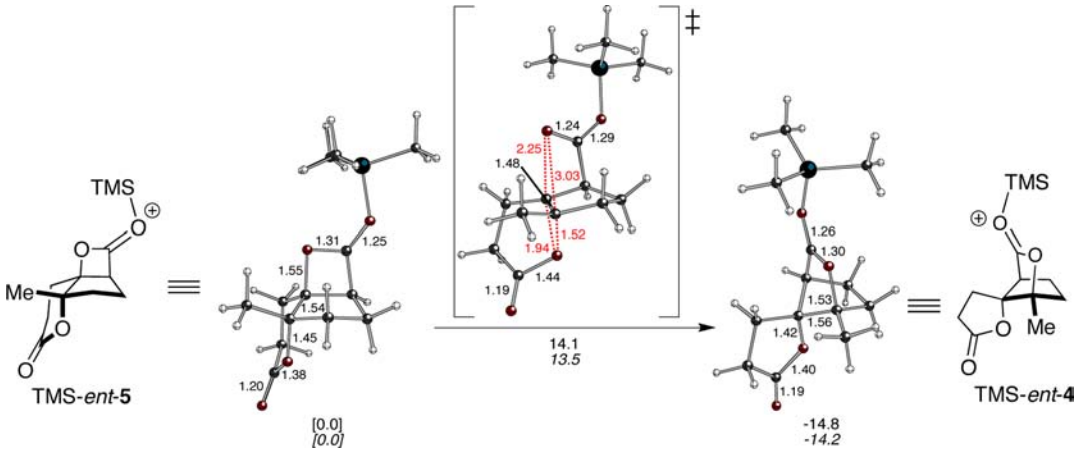


Figure 4. Computed geometries (B3LYP/6-31+G(d,p))[27] of species involved in the rearrangement of TMS-*ent*-**5** to TMS-*ent*-**4**. Energies shown are in kcal/mol and are relative to that of the reactant complex (ZPE-corrected energies in normal text; free energies at 25 °C in italics). Selected bond lengths are given in Å.

carbocations, making this intermediate difficult to intercept. Overall, the $\Delta G^{\ddagger}$ for the reaction with $Zn(OTf)_2$ was calculated to be 16 kcal/mol in the gas phase (<10 kcal/mol in CH_2Cl_2), and the product was calculated to be favored by 12 kcal/mol relative to the β-lactone− $Zn(OTf)_2$ reactant.

In contrast, examination of the TMSOTf-mediated rearrangement of the tricyclic β-lactone **16a** indicated that, unlike the Zn(II)-bound species, this species can undergo a low-barrier *concerted* dyotropic rearrangement (cf. **20**, Figure 3).[20] This reaction is predicted to have a barrier of only 6−7 kcal/mol in the gas phase (5 kcal/mol in CH_2Cl_2). These results indicate that the reaction can proceed readily at room temperature to produce the desired γ-lactone, despite the fact that only trace amounts of the γ-lactone product were observed experimentally using TMSOTf.

Dyotropic Rearrangements of Bis-lactones. We also examined the mechanism of the bis-lactone dyotropic rearrangement, which delivers the curcumalactone core (cf. Scheme 4). Related dyotropic rearrangements have been used in total synthesis efforts, with the most closely related being that by Fuchs in his strategy to cephalostatin analogues.[26] The TMSOTf-promoted rearrangement of (−)-**5** to (+)-**4** is predicted to be a concerted dyotropic rearrangement (Figure 4).[27] The barrier for this rearrangement is approximately 7 kcal/mol higher than that predicted previously for the analogous rearrangement of **16a**,[20] reflecting the different propensities of ester and acyl groups for migration. In addition, the transition state structure shown in Figure 4 also has shorter partial bonds to the migrating groups and a longer central C−C bond (1.48 vs 1.39 Å) than found for **16a**.[20] Thus, in contrast to the rearrangement of **16a**, in which substantial charge separation occurs (the transition state structure for this process resembles an acyl cation and a TMS-complexed carboxylate migrating across a partial double bond, cf. Figure 3, **20**), the rearrangement shown in Figure 4 more closely resembles a "double S_N2" process, in which a lone pair on each migrating oxygen attacks the backside of the other C−O bond. This picture is borne out by computed electrostatic potential maps for the structures in Figure 4. As shown in Figure 5, charge separation actually appears to decrease slightly as the transition state structure is reached. Silylation of the δ-lactone carbonyl is also possible and is actually favored by approximately 8 kcal/mol. Silylation is associated with an increase in double bond

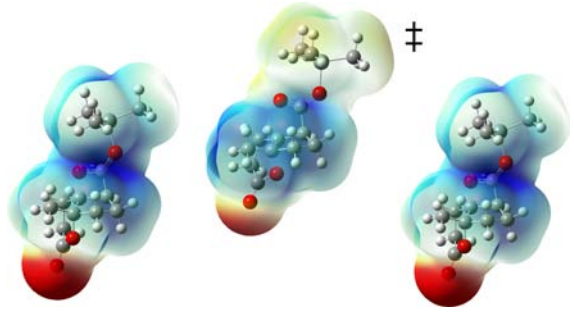


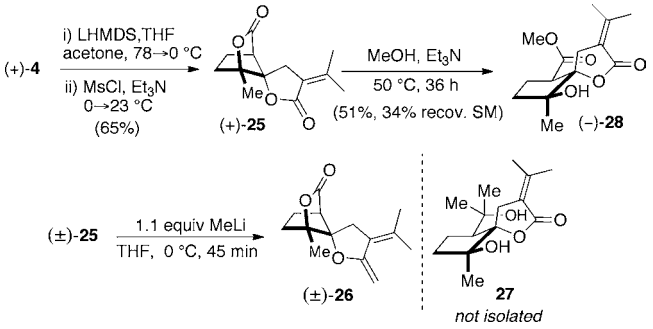
Figure 5. Electrostatic potential surfaces for the stationary points shown in Figure 4 (blue is most positive; charge range: 6.0×10^{-2} to 14.5×10^{-2}; isovalue: 0.0200).

character for the O−C bond within the δ-lactone ring and is accompanied by greater angle strain for the smaller β-lactone ring. However, the transition state structure for rearrangement of the resulting species is predicted to be approximately 5 kcal/mol higher in energy than that shown in Figure 4, and there appears to be greater strain associated with the former transition state structure, in contrast to the situation for the corresponding reactants.[28] If the β-lactone-complexed and δ-lactone-complexed reactants can interconvert under the reaction conditions, which seems plausible, then the Curtin−Hammett principle[29] is expected to apply, and the transition state structure in Figure 3 is expected to correspond to the predominant route to product.

Final Stages of the Synthesis of (−)-Curcumanolide A (1) and (−)-Curcumalactone (3). We recognized that the reactivity of the two γ-lactones present in the bis-lactone (+)-**4** would require further differentiation to enable selective ring cleavage of the bridged γ-lactone. We thus chose to introduce the required β,β'-dimethyl enoate at an early stage to further differentiate the reactivity of these two γ-lactones. Thus, aldol condensation with acetone in a two stage, one-pot reaction provided the desired enoate (+)-**25** in 65% yield (Scheme 5). In efforts to directly form the isopropylidene precursor **27** by nucleophilic addition to the more strained, bridged, γ-lactone over the less electrophilic α,β-unsaturated lactone, we first tested a variety of conditions to generate tertiary alcohol **27** via methyllithium or methyl Grignard addition. In early studies with racemic bis-lactone (±)-**25**, treatment with 1.1 equiv MeLi

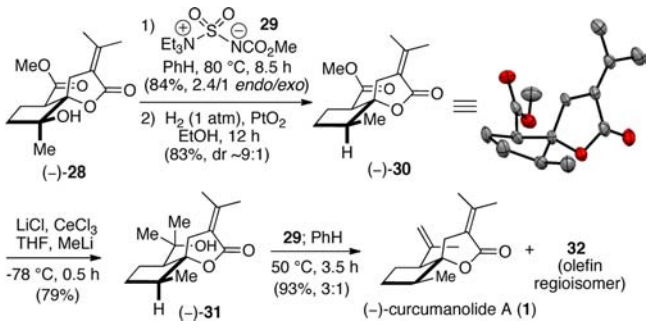
dx.doi.org/10.1021/ja303414a | J. Am. Chem. Soc. 2012, 134, 13348−13356

Scheme 5. Aldol Addition/Elimination and Selective Ring-Opening of Bis-lactone (+)-25[a]



[a]LHMDS, lithium bis(trimethylsilyl)amide; MsCl, methanesulfonyl chloride.

Scheme 6. Conversion of Methyl Ester (−)-28 to the Common Core (−)-31 and Synthesis of (−)-Curcumanolide A (1)[a]

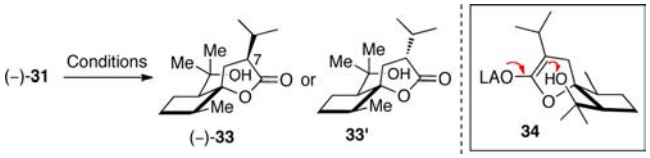


[a]Inset: ORTEP representation of the X-ray crystal structure of spirolactone (−)-**30**; hydrogens removed for clarity; thermal ellipsoids shown at 50% probability.[32]

did not deliver tertiary alcohol **27** but rather yielded dienyl tetrahydrofuran **26**, presumably formed by 1,2-addition and subsequent alcohol elimination during the mild acid work-up. Reaction with Grignard reagents (MeMgI or MeMgBr) gave a mixture of recovered starting material and both mono- and bis-addition products as judged by analysis of crude ^{1}H NMR. As an alternative, we next considered ring cleavage to a methyl ester for subsequent conversion to the tertiary alcohol. Employment of standard methanolysis conditions (NaOMe, MeOH) provided some desired ester, but also the diester from cleavage of both γ-lactones. However, use of Et_3N in MeOH under reflux conditions gave the desired hydroxy ester (−)-**28** in modest yield with only trace amounts of the diester, and finally a decrease in reaction temperature to 50 °C provided exclusively the desired product in serviceable yield (51%) and good recovery of starting material (34%).[30] Longer reaction times and increased amounts of Et_3N led to similar results, suggestive of reversible ring-opening of the two γ-lactones under these conditions.

To install the C4-methyl-bearing stereocenter, we envisioned dehydration of the secondary alcohol of (−)-**28** at C4 followed by a facially selective hydrogenation of the more sterically accessible face syn to the C−O bond of the spirolactone (Scheme 6). A number of standard alcohol elimination products were screened at various temperatures including $SOCl_2/Et_3N$, $SOCl_2$/pyridine, $MsCl/Et_3N$, $MsCl/Et_3N$/DBU, or MsCl/DMAP/pyridine and performed well on small scale;

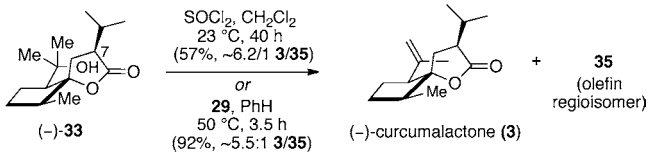
Table 3. Conditions Tested for the Diastereoselective, Substrate-Directed Reduction of Enoate (−)-31 to (−)-33



entry	conditions	% yield (dr, **33**:**33**′)
1	5 mol % PtO_2, EtOH, 35 bar H_2, 48 h[a]	55 (<1:19)[b]
2	CuBr, Red-Al, THF, 0 °C, 2 h	ND (3:1)[c]
3	L-Selectride, THF, −78 °C → 0 °C, 1.5 h	83 (>19:1)[b]

[a]Use of EtOAc as solvent gave similar results. [b]Isolated yield after column chromatography. [c]Ratio determined by ^{1}H NMR analysis of crude reaction mixture. Yield not determined (ND).

Scheme 7. Dehydration of Tertiary Alcohol 33 Leading to (−)-Curcumalactone (3)



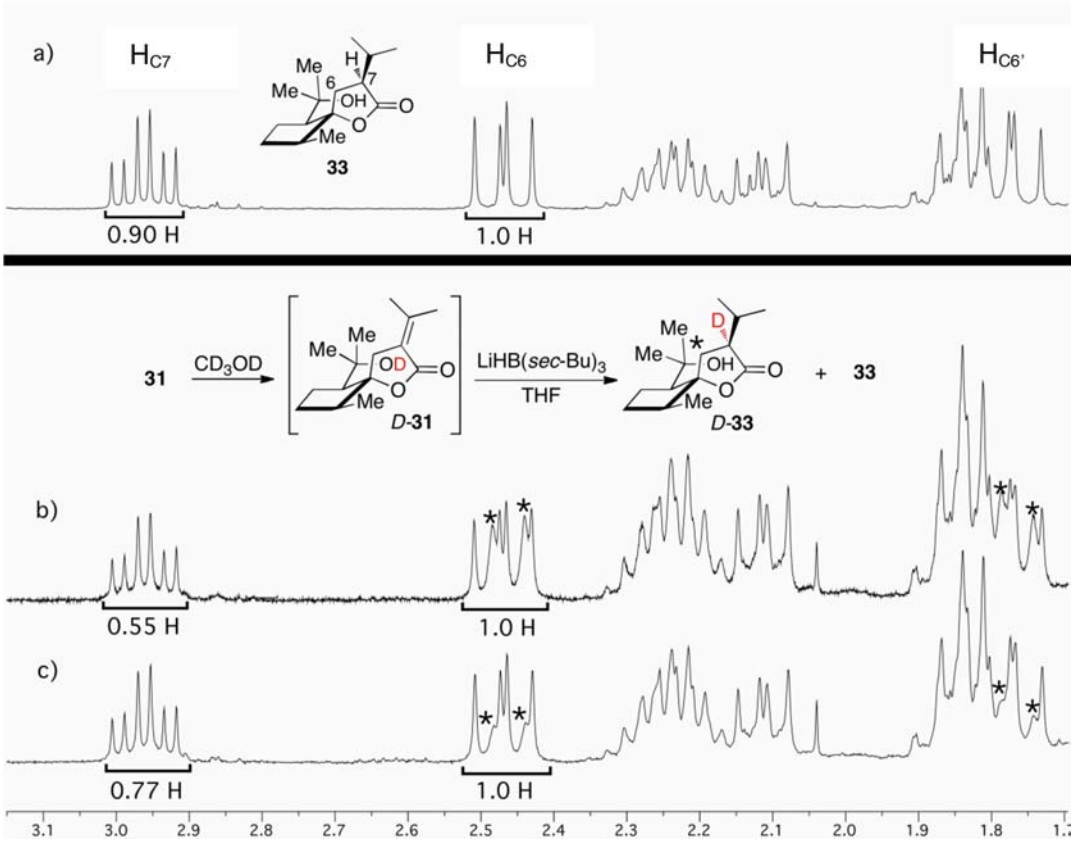
however, these reagents were inferior, leading to low conversion on scale-up. Ultimately, Burgess' reagent (**29**)[31] in refluxing benzene was found to give high yields (84%) of an inseparable *exo*/*endo* mixture (2.4:1) of olefinic products. Several conditions were screened for the required olefin reduction, including diimide reduction, and hydrogenation with Pd/C and Wilkinson's catalyst ($Rh(PPh_3)_3Cl$); however, these conditions gave low conversion. Ultimately, hydrogenation with 5 mol % PtO_2 led to complete reduction at 1 atm H_2 after 12 h with good facial selectivity (83% yield, ~9:1 dr). The stereochemistry of the major diastereomer (−)-**30** was confirmed by X-ray analysis supporting the anticipated facial selectivity providing the desired C4 stereochemistry. The minor diastereomer obtained during this hydrogenation possesses the relative stereochemistry found in curcumanolide B.

We next turned our attention to conversion of the methyl ester to an isopropylidene group (Scheme 6). Selective addition of Grignard reagents to the methyl ester over the spirolactone was initially studied with MeMgI and MeMgBr under a variety of conditions but all led to complex mixtures of products that included monoaddition to the ester, and both 1,4- and 1,2-addition to the spirolactone. The use of $CeCl_3$ as an additive[33] and subsequently $CeCl_3/LiCl$[34] had profoundly beneficial effects, and ultimately the use of MeLi rather than MeMgI or MeMgBr[35] led to efficient conversion to the desired tertiary alcohol (−)-**31** in 79% yield. The final dehydration toward (−)-curcumanolide A was accomplished by employing Burgess' reagent (**29**) once again under conditions similar to those previously reported by Kato,[6b] providing a 93% yield of a ~3:1 mixture of curcumanolide A (**1**, major product) and the corresponding exocyclic olefin regioisomer **32** (not shown). Partial separation of this mixture could be achieved by column chromatography providing pure (−)-curcumanolide A, and characterization data including optical rotation correlated well with previously reported data.[1]

In strategies toward curcumalactone, a key challenge posed is setting the stereochemistry at C7 (cf. **33** in Table 3). Previous synthetic studies typically led to the incorrect diastereomer at

dx.doi.org/10.1021/ja303414a | J. Am. Chem. Soc. 2012, 134, 13348−13356

Scheme 8. ^{1}H NMR Data (300 MHz) Supporting Intramolecular Protonation during Reduction with L-Selectride: (a) ^{1}H NMR Expansion (δ 1.7−3.15) of Saturated Lactone 33 for Comparison and Same Expansion Following Initial Deuterium Exchange of Tertiary Alcohol with CD_3OD for (b) 17 h and (c) 4 h, Leading to Deuterated 33 (D-33) in Different Ratios[a]



[a]Ratio of D incorporation based on integration: (b) ∼50% and (c) ∼30% D. Diastereotopic C6-protons going from two doublet of doublets to two doublets due to deuteration at C7 are marked by asterisks.

C7 through reduction of related enoate intermediates or direct alkylation leading primarily to C7-*epi*-curcumalactone. Thus, a subsequent epimerization was required to achieve, at best, a mixture of diastereomers.[6b] Given the presence of the tertiary alcohol in intermediate **31**, we considered two approaches to set the C7-stereochemistry. The first involved a possible hydroxyl-directed hydrogenation[36] of the tetra-substituted olefin, a process not without precedent.[37] However, the tetrasubstituted and electron-poor olefin in **31** was recalcitrant to hydrogenation with multiple catalysts under various conditions (Pd/C, $Pd(OH)_2$/C, $Pd/BaSO_4$,[37a] and Crabtree's catalyst) including high pressure (up to 35 bar H_2). Only when employing PtO_2 at 35 bar H_2 was reduction possible, providing 55% yield with 41% recovered starting material (Table 3, entry 1). This led to high diastereoselectivity for **33′** based on comparison with previously described C7-*epi*-curcumalactone,[6b] obtained following alcohol elimination of **33′**, indicating that the hydroxyl group was not directing the hydrogenation. A second strategy would make use of the tertiary alcohol in a different capacity. We considered the possibility of a 1,4-conjugate reduction followed by intramolecular protonation of the intermediate enolate by the tertiary alcohol in a facially selective fashion to deliver curcumalactone (cf. **34** in Table 3). Initially, reaction with the copper-hydride species generated in situ from CuBr and Red-Al[38] led to an ∼3:1 mixture of **33**/**33′**, indicating that some intramolecular protonation had likely occurred, but also some possible coordination of the tertiary alcohol with the cuprate species as described previously in the literature.[39] Ultimately, we discovered that 1,4-reduction with L-selectride in THF at −78 °C followed by warming to 0 °C and quenching at that temperature indeed led to the desired diastereomer **33** in high diastereoselectivity and yield (dr >19:1, 83%).

The synthesis of (−)-curcumalactone was completed by dehydration employing $SOCl_2$ following the method of Kato[6b] to deliver an ∼6.2:1 mixture of *endo*/*exo* olefin regioisomers in 57% yield (Scheme 7). This elimination could also be performed with Burgess' reagent in higher yields with slightly decreased ratios of curcumalactone and the corresponding endo regioisomer (92%, ∼5.5:1 **3**/**35**).[6b] Purification by column chromatography delivered pure (−)-curcumalactone and both spectral and optical rotation data correlated well with reported values.[6]

The high diastereoselectivity observed from conjugate reduction of enoate **31** with L-Selectride is noteworthy and points to the likelihood of an *intramolecular* protonation of an intermediate boron enolate since the diastereomeric product **33′** would be expected from an *intermolecular* protonation of the enolate **34** (Table 3). We designed an experiment to probe the hypothesis that intramolecular protonation by the adjacent tertiary alcohol (i.e. via enolate **34**, Table 3) was indeed occurring following conjugate reduction. Intramolecular protonation of enolates by alcohols has been described in the literature,[40] and the preferred conformation of the spirocyclic

dx.doi.org/10.1021/ja303414a | J. Am. Chem. Soc. 2012, 134, 13348−13356

system (i.e., **31**) appeared conducive for such an intramolecular protonation (see **34**, Table 3). We reasoned that alcohol OH → OD exchange with excess CD_3OD, followed by azeotropic drying with xylenes and reduction with L-selectride, would lead to deuterated species D-**33** (Scheme 8). This process gave varying amounts of D-**33** depending on the time allowed for H → D exchange (4 vs 17 h, Scheme 8b,c); however, high diastereoselectivity was consistently observed, suggestive of an intramolecular protonation/deuteration. Incorporation of deuterium at C7 is evidenced by simplification of the diastereotopic C6-protons (indicated by *) from two sets of doublet of doublets (dd, J = 10.5, 13.2) to a doublet (d, J = 13.2) centered at δ 2.47, due to exchange of a vicinal proton at C7 for deuterium. Similar simplification is also observed with the diastereotopic C6′ proton centered at δ 1.77 but is obscured by other protons. Further confirmation of deuterium incorporation came from HRMS analysis of the mixture of **33**/D-**33**.[28] The inability to achieve complete deuterium incorporation is not easily explained, given the high facial selectivity that excludes intermolecular processes, but the simplest explanation is incomplete deuterium exchange of the tertiary alcohol. Importantly, this sequence provides a highly stereocontrolled introduction of the C7 stereocenter, a challenge encountered in the previous synthesis of curcumalactone.[6b]

CONCLUSIONS

In summary, we provided a full account of our recently disclosed stereospecific dyotropic process to spirocyclic, bridged γ-butyrolactones via Lewis-acid-mediated 1,2-acyl and δ-lactone migrations. By employing these methods, concise asymmetric routes to the spirocyclic sesquiterpene natural products (−)-curcumanolide A and (−)-curcumalactone have been accomplished through a key dyotropic process of a tricyclic β,δ-bis-lactone, which establishes the spirocyclic stereocenter. DFT calculations on this dyotropic rearrangement suggest a double 'S_N2-like' process of the two migrating carboxylates with a diminution in charge separation as the transition state structure is reached. The synthesis demonstrates the utility of our catalytic, asymmetric NCAL process and the ability to perform a Baeyer−Villiger oxidation in the presence of a β-lactone. A highly diastereoselective 1,4-reduction involving intramolecular protonation by a resident tertiary alcohol established the final stereocenter found in curcumalactone. The described enantioselective synthesis of curcumanolide A and curcumalactone was accomplished in 11 and 12 steps, respectively, from 2-methyl-1,3-cyclopentanedione and did not require the use of protecting groups. The synthetic strategy described herein provides efficient routes to both natural products, enabling further biological studies of these potentially bioactive spirolactones.

ASSOCIATED CONTENT

Supporting Information

Complete ref 27d. Complete experimental and characterization details for all new compounds reported, along with additional details on calculations. Crystallographic files. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful for generous support from the National Science Foundation (CHE-0809747 to D.R., CHE-0755207 REU supporting A.G.J., CHE-0449845 and CHE-030089 (Pittsburgh Supercomputer Center) to D.J.T., and the Welch Foundation (A-1280 to D.R.). We thank Dr. Joe Reibenspies for the X-ray analyses and Dr. Arjun Raghuraman for technical assistance.

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