# Enantioselective Synthesis of (−)-Wikstromol Using a New Approach via Malic Acid

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*Received November 1, 2000*

The total synthesis of (−)-wikstromol, a bioactive α-hydroxylated lactone lignan, from natural malic acid using a consecutive alkylation strategy is presented. First, alkylation of a malic acid ester provided the monobenzyl derivative, which was then converted to an α-substituted dioxolanone. This derivative was reacted in a second alkylation step to a double benzylated dioxolanone, which was transformed to bis-*O*-benzyl-protected (−)-wikstromol and subsequently to the natural product. Only six steps were required to produce wikstromol in 30% overall yield. A second approach from malic acid, the double alkylation of dienolates from 5-oxo-1,3-dioxolan-4-yl acetic acid derivatives, was not successful. No reaction conditions were found to afford the dienolates. Instead, rapid fragmentation of the dioxolanones to fumaric acid derivatives and pivalaldehyde occurred even at −105 °C, and aldol reaction products with good stereoselectivity were formed. The relative configuration of the major isomer was determined by X-ray structure analysis. By comparison of NMR data it is shown that a previous assignment of the configuration of one of the described aldol products was incorrect.

## Introduction

The enantiomers of wikstromol **1**,[1,2] also called nortrachelogenin[3] or pinopalustrin,[4] are widely distributed in Asian medicinal plants.[5,6] They belong to the class of the relatively rare α-hydroxylated lactone lignans[7] and exhibit several biological activities,[8] among which the antileukemic activity in vivo is most important.[8b] Despite their biological properties, only one total synthesis of either enantiomer of wikstromol has been published so far. Brown et al. reported an eight-step synthesis of (+)-**1** and of (−)-**1** over a decade ago.[9] The major drawbacks of these syntheses were the resolution of a racemic precursor and a nonselective oxygenation α to the carbonyl group in the penultimate step. As a result, the overall yields of (+)- and (−)-**1** were 5 and 6%, respectively. A more efficient synthesis of *rac*-**1** (overall yield 29%, nine steps) was published by Belletire and Fry in 1988.[10]

Herein we report a short and efficient synthesis of (−)-wikstromol (**1**) starting from (−)-malic acid (**2**) as chiral precursor (Scheme 1).

## Results and Discussion

**(1) The Dienolate Approach.** More than 20 years ago, Garett et al. showed that 1,3-diene-1,4-diolates (dienolates), produced by double deprotonation of 1,4-dicarbonyl compounds, are highly reactive nucleophiles which can be double alkylated in one step.[11] This strategy was later used to synthesize different types of lignans as racemates.[12,13] For an enantioselective synthesis of wikstromol (**1**), which has two equally substituted benzyl groups, a double alkylation of an optically active dienolate, derived from a dioxolanone, would be an attractive route (Scheme 2). Since dioxolanone dienolates were

† Fax: +49 331 977 5067.

(1) Tandon, S.; Rastogi, R. P. *Phytochemistry* **1976**, *15*, 1789−1791.

(2) For a discussion of the stereochemical differences in the biosynthesis of (+)- and (−)-**1**, see: Umezawa, T.; Okunishi, T.; Shimada, M. *ACS Symp. Ser.* **1998**, *697*, 377−388.

(3) Nishibe, S.; Hisada, S.; Inagaki, I. *Phytochemistry* **1971**, *10*, 2231−2232.

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(6) Nonmedicinal plants: (a) Su, W.-C.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1995**, *40*, 563−566. (b) Lin, W.-H.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1999**, *50*, 653−658. (c) Kawai, S.; Sugishita, K.; Ohashi, H. *Phytochemistry* **1999**, *51*, 243−247. (d) Lin, T.-C.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1999**, *51*, 793−801.

(7) (a) Ayres, D. C.; Loike, J. D. *Lignans Chemical, biological and clinical properties*, Cambridge University Press: Cambridge, **1990**. (b) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75−96 and previous reviews of this series.

(8) (a) Torrance, S. J.; Hoffmann, J. J.; Cole, J. R. *J. Pharm. Sci.* **1979**, *68*, 664−665. (b) Lee, K.-H.; Tagahara, K.; Suzuki, H.; Wu, R.-Y.; Haruna, M.; Hall, I. H.; Huang, H.-C.; Ito, K.; Iida, T.; Lai, J.-S. *J. Nat. Prod.* **1981**, *44*, 530−535. (c) Ji-Xian, G.; Handa, S. S.; Pezzuto, J. M.; Kinghorn, A. D.; Farnsworth, N. R. *Planta Med.* **1984**, *50*, 264−265. (d) Suga, T.; Ohta, S.; Munesada, K.; Ide, N.; Kurokawa, M.; Shimizu, M.; Ohta, E. *Phytochemistry* **1993**, *33*, 1395−1401. (e) Lin, R. C.; Skaltsounis, A.-L.; Seguin, E.; Tillequin, F.; Koch, M. *Planta Med.* **1994**, *60*, 168−170. (f) Nishibe, S. *Pure Appl. Chem.* **1994**, *66*, 2263−2266. (g) González, J. A.; Estévez-Braun, A.; Estévez-Reyes, R.; Bazzocchi, I. L.; Moujir, L.; Jiminez, I. A.; Ravelo, A. G.; González, A. G. *Experientia* **1995**, *51*, 35−39.

(9) (a) Khamlach, K.; Dhal, R.; Brown, E. *Tetrahedron Lett.* **1989**, *30*, 2221−2224. (b) Khamlach, M. K.; Dhal, R.; Brown, E. *Tetrahedron* **1992**, *46*, 10115−10126.

(10) (a) Belletire, J. L.; Fry, D. F. *J. Org. Chem.* **1988**, *53*, 4724−4729. (b) Belletire, J. L.; Ho, D. M.; Fry, D. F. *J. Nat. Prod.* **1990**, *53*, 1587−1592.

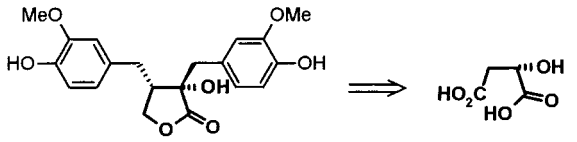
(11) Garratt, P. J.; Zahler, R. *J. Am. Chem. Soc.* **1978**, *100*, 7753−7754.

(12) Pohmakotr, M.; Reutrakul, V.; Prongpradit, T.; Chansri, A. *Chem. Lett.* **1982**, 687−690.

(13) Mahalanabis, K. K.; Mumtaz, M.; Snieckus, V. *Tetrahedron Lett.* **1982**, *23*, 3975−3978.

10.1021/jo001547z CCC: $20.00 
Published on Web 03/06/2001

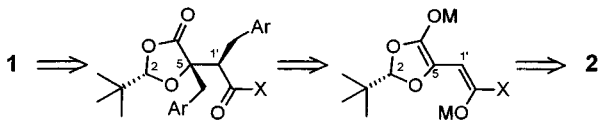
**Scheme 1**




(-)-wikstromol **1**
[(-)-nortrachelogenin]

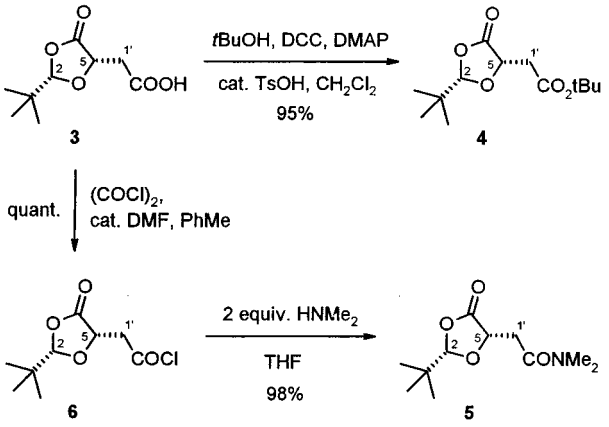
(-)-malic acid **2**

**Scheme 2**




M = Li, Na, K
X = OR, SR, $NR_2$

**Scheme 3**

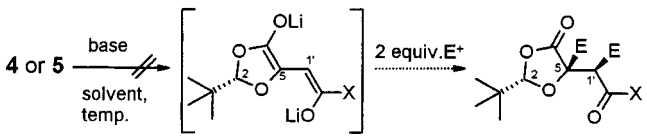



hitherto unknown intermediates, the stability and geometry of these dienolates and the stereochemistry of their reaction products were first examined.

Starting material for our investigations was dioxolanone **3** (Scheme 3). This compound was deprotonated and alkylated selectively at C(5), as demonstrated by Seebach et al.[14] C(1′) was "protected" from alkylation due to the formation of a lithium carboxylate. Thus, for the development of a double deprotonation/alkylation strategy, *tert*-butyl ester **4**[15] and dimethylamide **5** were synthesized as substrates (Scheme 3). Ester **4**, obtained in 95% yield from dioxolanone **3** using a modified Steglich esterification protocol,[16] was chosen because of its steric hindrance and selective removal under mild conditions. However, it was shown that 1,4-bis-dialkylamides provide more stable dienolates than the corresponding esters.[17] Thus, dimethylamide **5** was prepared in a two-step sequence via acyl chloride **6** (98% yield from **3**).

Dioxolanones **4** and **5** were treated with 2 equiv of lithium amide bases; thereafter various electrophiles were added in excess (Scheme 4 and Table 1). Unfortunately, addition of 2 equiv of lithium diisopropylamide (LDA) to dioxolanone **4** at −71 °C and quenching after 15 min with trimethylsilyl chloride (TMS-Cl) afforded complete decomposition (Table 1, entry 1). The same

**Scheme 4**



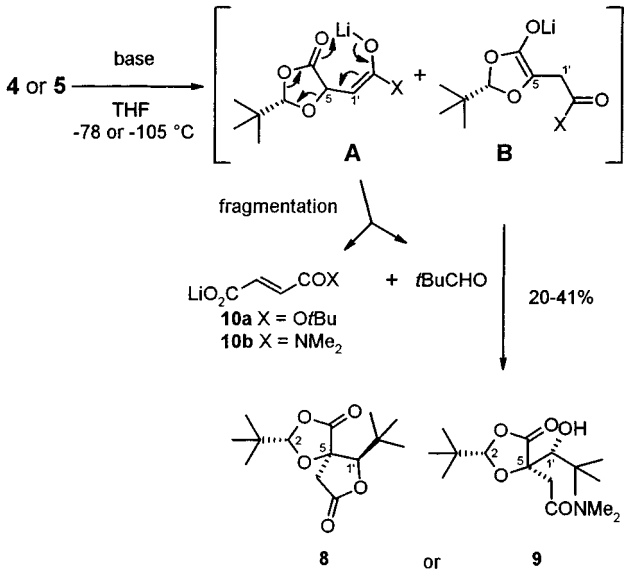

X = O*t*Bu, X = $NMe_2$

**Table 1. Conditions for the Attempted Double Deprotonation of Dioxolanones 4 and 5**

| entry | compd | base (equiv) | *T* [°C] | *t* [min][a] | $E^+$ | products |
|---|---|---|---|---|---|---|
| 1 | **4** | LDA (2)[b] | −71 | 15 | TMS-Cl | decomp |
| 2 | **4** | LDA (2) | −78 | 0 | **7**[c] | decomp |
| 3 | **4** | LHMDS (2) | −78 | 10 | DCl | **8** (20%) |
| 4 | **5** | LDA (2) | −78 | 10 | **7**[c] | **9** (25%) |
| 5 | **5** | LDA (2) | −105 | 15 | DCl | **9** (30%) |
| 6 | **5** | LHMDS (2) | −78 | 15 | DCl | **9** (41%) |
| 7 | **5** | LHMDS (2) | −105 | 0 | **7**[c] | **9** (35%) |
| 8 | **5** | LHMDS (2) | −105 | 0 | TMS-Cl | decomp |
| 9 | **5** | LHMDS (1) | −103 | 0 | **7**[c] | **9** (30%) |

[a] Addition of the electrophile after *x* min; 0 min means metalation of the dioxolanones in the presence of the electrophile. [b] Base precooled to −75 °C. [c] Compound **7**: 4-benzyloxy-3-methoxybenzyl bromide (Scheme 9).

**Scheme 5**




result was obtained when **4** was deprotonated (LDA, −78 °C) in the presence of 3 equiv of 4-benzyloxy-3-methoxybenzyl bromide (**7**) as electrophile (entry 2). In both cases no starting material was recovered, indicating complete conversion of **4**. Metalation of **4** with 2 equiv of lithium hexamethyldisilazide (LHMDS), under otherwise similar deprotonation conditions, afforded spirolactone **8** (Scheme 5) in 20% yield and >20:1 diastereoselectivity (entry 3). An analogous aldol product, alcohol **9** (Scheme 5), was obtained when amide **5** was treated with 2 equiv of LDA or LHMDS and reacted with DCl or **7** (entries 4−7). Neither deuterated nor alkylated malic acid derivatives were formed under any conditions tested. In all cases, aldol product **9** was isolated in an up to 40% yield and with good diastereoselectivity (>10:1).[18] Decomposition occurred even if dioxolanone **5** was metalated below −105 °C in the presence of TMS-Cl (entry 8). Treatment of amide **5** with 1 equiv of LHMDS, to afford a C(5)-monoalkylated compound, yielded again aldol product **9** (30%) (entry 9).

(14) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313−1324.
(15) Tain, Z.-Q.; Brown, B. B.; Mack, D. P.; Hutton, C. A.; Bartlett, P. A. *J. Org. Chem.* **1997**, *62*, 514−522.
(16) Krohn, K.; Meyer, A. *Liebigs Ann. Chem.* **1994**, 167−174.
(17) Mahalanabis, K. K.; Mumtaz, M.; Snieckus, V. *Tetrahedron Lett.* **1982**, *23*, 3971−3974.

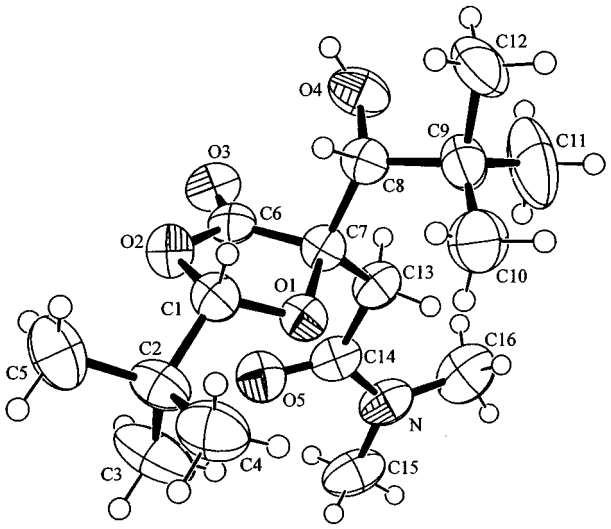



**Figure 1.** X-ray crystal structure of amide **9**.[35]

The formation of **8** and **9** can be explained if one assumes that deprotonation at C(5) or at C(1′) occurred with similar reaction rates and is supported by the findings using 1 equiv of base (entry 9 of Table 1), in which enolates **A** and **B** were provided (Scheme 5). Instead of a subsequent α-deprotonation at the second available center, enolate **A** underwent a rapid *β*-elimination, even at −105 °C, producing the lithium salt of fumaric acids **10** (isolated as the corresponding acids) and pivalaldehyde. The aldehyde then reacted, as soon as liberated, with enolate **B** to give aldol product **9** in good yields, when compared to a maximum yield of 50% for that reaction type.

The absolute configuration of the major isomers of spirolactone **8** and amide **9** was determined to be 2*S*,5*R*,1′*R*, based on the known configuration of malic acid and confirmation of the relative configuration by an X-ray structure analysis of amide **9** (Figure 1).[18]

According to Seebach et al.,[14] aldol reaction of pivalaldehyde with the enolate of dioxolanone **3** gave preferentially spirolactone **11** with a 2*S*,5*R*,1′*S* configuration. The formation of lactones **8** and **11**, epimers at C(1′), obtained either from decomposition of ester **4** or aldol reaction of acid **3**, leads to the conclusion that these two reactions follows different stereochemical courses. However, a comparison of the chemical shifts reported for **11**[14] with those obtained for **8** revealed no differences. Therefore, aldol reaction[14] of dioxolanone **3** with pivalaldehyde was carried out to compare the ratios of spirolactones **8** and **11** formed by either decomposition of **4** or aldol reaction of **3** (Scheme 6 and Table 2).

As described above, fragmentation of ester **4** with LHMDS provided spirolactones **8** and **11** in a ratio better than 20:1 (Table 2, entry 1). Surprisingly, the reaction of the dioxolanone of **3** with pivalaldehyde gave preferentially lactone **8** with diastereoselectivities of 5:1 (LDA) and 5:2 (LHMDS), respectively (entries 2 and 3).[19] Additionally, a third diastereoisomer, **12**, was found under these conditions (entries 2−4, relative configuration not determined). The selectivity for **8** increased when the reaction was carried out at −105 °C using 3 equiv of LDA (entry 4). The increase in stereoselectivity was due to the lower reaction temperature and/or partially to the fragmentation mechanism, in which 3 equiv of base was used.[20]

**Scheme 6**

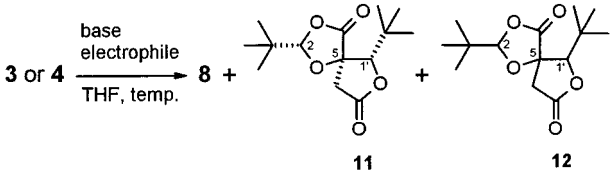
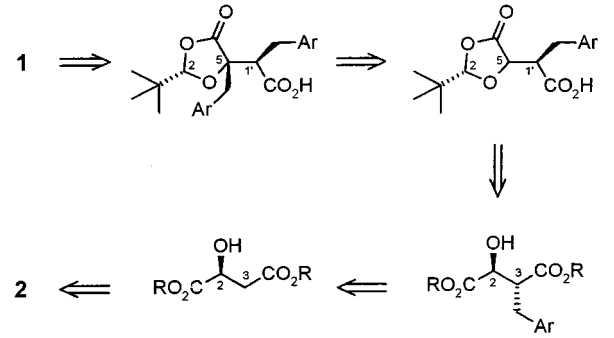



**Table 2. Stereoselectivities for 8, 11, and 12 Obtained via Aldol Reaction of 3 or Fragmentation of 4**

| entry | compd | base (equiv) | electrophile | *T* [°C] | yield [%] | **8**:**11**:**12** |
|---|---|---|---|---|---|---|
| 1 | **4** | LHMDS (2) | | −78 | 20 | >20:1:−[a] |
| 2 | **3** | LDA (2) | *t*BuCHO | −78 | 52 | 5:1:1 |
| 3 | **3** | LHMDS (2) | *t*BuCHO | −78 | 44 | 5:2:1 |
| 4 | **3** | LDA (3) | *t*BuCHO | −105 | 47 | 10:1:1 |

[a] Not detectable.

**Scheme 7**




**(2) The Consecutive Alkylation Approach.** The formation of optically active, dioxolanone-based dienolates was not successful, and therefore, a consecutive alkylation strategy was developed for a short synthesis of (−)-wikstromol (**1**) from (−)-malic acid (**2**), as depicted in Scheme 7. An analogous approach from malic acid was recently reported for the enantioselective total synthesis of (−)-meridinol. Disadvantages of this synthesis were a reduction/reoxidation sequence and an almost unselective second alkylation affording the natural product in only 3.3% overall yield over eight steps.[21]

The major challenge of our consecutive alkylation strategy was the preparation of a C(1′)-benzyl-substituted dioxolanone and its stereoselective alkylation at C(5), which has not yet been reported and for which the stereochemical outcome was uncertain, due to the additional stereocenter in the side chain.

The first alkylation reaction for the synthesis of **1** was the diastereoselective benzylation of a malic acid ester.

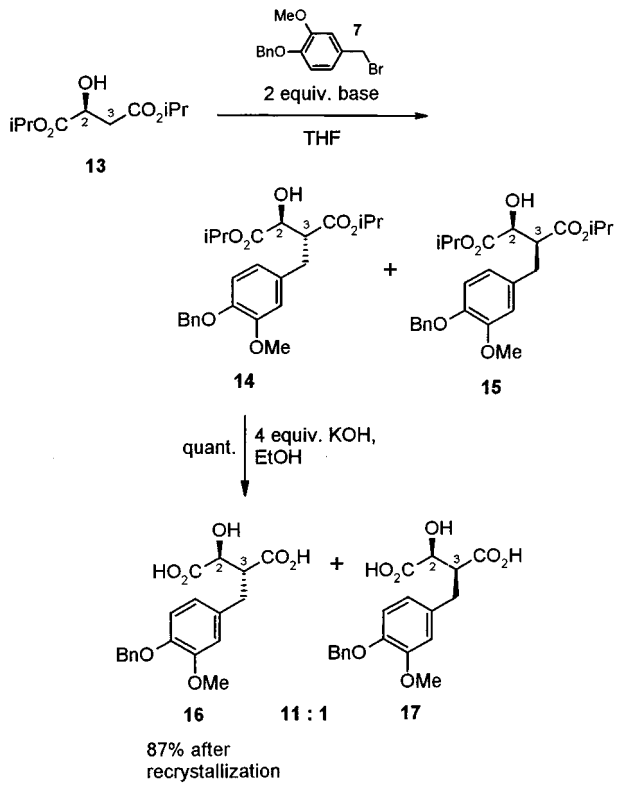
(18) Amides **9** and *epi*-**9** have very different $R_f$ values (TLC). Compound **9** is even less polar than the starting material **5**, despite the additional hydroxy group. We assumed that an intramolecular hydrogen bridge bonding to the amide carbonyl group is responsible for the low polarity of this amide, but no evidence was provided by the X-ray structure of **9** (Figure 1).

(19) The diastereomers **8** and **11** had very different chemical shifts in proton and carbon NMR. Thus, having established the configuration of **8**, the chemical shifts reported in the literature correspond to **8** and not to the 1′*R* epimer **11**.[14]

(20) Alkylation of dioxolanone **3** with benzyl bromide using 2.3 equiv of LHMDS afforded, besides the benzylation product (66%), 15% of a 10:1 mixture of **8** and **11**. This result proved that fragmentation of **3** is possible if more than 2 equiv of base were used.

(21) Takano, D.; Doe, M.; Morimoto, Y.; Yoshihara, K.; Kinoshita, T. *J. Heterocycl. Chem.* **1999**, *36*, 221−224.

**Scheme 8**



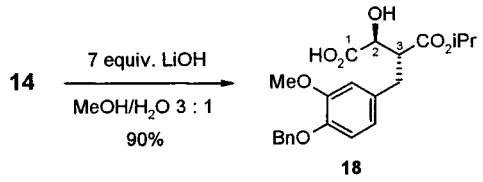

This reaction was first reported 20 years ago by Seebach and Wasmuth[22] and was well established for the preparation of enantiopure succinic acid derivatives.[23] Commercially available (−)-diisopropyl malate (**13**)[24,25] was reacted with benzyl bromide **7** using two modifications of the standard protocol:[26] (1) LHMDS was used as base instead of LDA, because superior diastereoselectivities were reported for the *threo*-configurated alkylation products if enolization was induced by LHMDS[27] and (2) malate **13** was deprotonated in the presence of electrophile **7** at −75 °C (Scheme 8). At this temperature only 10% of alkylation products **14** and **15** were formed after 14 h[28] and warming to +10 °C was required to achieve best results (80% yield, ratio of **14**: **15** = 15:1).

Although different amide bases were used for the alkylation of malates, $Li^+$ was always the counterion. The role of the counterion, often pivotal for good stereoselectivities,[27] was examined for the transformation of **13** to **14**/**15** by using sodium hexamethyldisilazide (NHMDS) and potassium hexamethyldisilazide (KHMDS) as bases (Table 3). Alkylation of **13** using KHMDS was very sluggish, providing **14** and **15** in a 1:1 ratio and in low yield (20%). Enolization with NHMDS proceeded smoothly but a reversed ratio of **14** and **15** (1:2) was found, and the yield of alkylation products was moderate (45%).[30]

**Table 3. Alkylation of Diisopropyl Malate 13 Using Different Alkali Metal Bases**

| entry | base | yield [%] | **14**:**15** |
|---|---|---|---|
| 1 | LHMDS | 80 | 15:1 |
| 2 | NHMDS | 45 | 1:2 |
| 3 | KHMDS | 20 | 1:1 |

**Scheme 9**




Diastereoisomers **14** and **15** were separated by column chromatography. The major isomer **14** was saponified with 4 equiv of KOH in EtOH, providing the two diastereoisomers **16** and **17** in quantitative yield and in a ratio of 11:1 (Scheme 8). Recrystallization from $CHCl_3$ containing small amounts of MeOH afforded acid **16**, diastereomerically pure, in 87% yield.

The partial epimerization, which occurred during saponification of **14**, should be avoided if the less basic LiOH in water/methanol mixtures is used instead of KOH in EtOH. Unfortunately, only a C(1)-selective monosaponification of **14** occurred, even with a large excess of LiOH (7 equiv) and a longer reaction time (3 days), producing monoester **18** in 90% yield (Scheme 9) without epimerization at C(3).

Acid-catalyzed acetalization of diacid **16** with pivalaldehyde proceeded smoothly if benzene was used as solvent, and removal of water was accomplished using a Soxhlet apparatus, filled with activated 4 Å molecular sieves (Scheme 10). Other methods (a Dean−Stark trap, other solvents,[31] or protic catalysts) were not successful. Both, *trans*-dioxolanone **19** and *cis*-dioxolanone **20** were obtained in over 80% yield and in a ratio of approximately 1:5, which is similar to a previously reported ratio for dioxolanone **3** and its *trans*-epimer using the same solvent.[31] Recrystallization of the diastereoisomeric mixture from EtOH/water afforded **20**, diastereomerically pure, in 70% yield.

The second alkylation step was performed by deprotonation of **20** with 2 equiv of LHMDS at −72 °C in the presence of electrophile **7**.[14] The intermediate C(4)−C(5)-

(22) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197−200.

(23) Recent examples: (a) Whittingham, W. G.; Ellis, M. K.; Guerry, P.; Henderson, G. B.; Müller, B.; Taylor, D. A.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Chem. Commun.* **1989**, 1116−1119. (b) Gosh, A. K.; Thompson, W. J.; Fitzgerald, P. M. D.; Culberson, J. C.; Axel, M. G.; McKee, S. P.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1994**, *37*, 2506−2508. (c) Schmitz, C.; Rouanet-Dreyfuss, A.-C.; Tueni, M.; Biellmann, J.-F. *J. Org. Chem.* **1996**, *61*, 1817−1821.

(24) Diastereoselective alkylations of **13** have been reported: (a) Miller, M. J.; Bajwa, J. S.; Mattingly, P. G.; Peterson, K. *J. Org. Chem.* **1982**, *47*, 4928−4933. (b) Bajwa, J. S.; Miller, M. J. *J. Org. Chem.* **1983**, *48*, 1114−1116.

(25) The beneficial effect of the isopropyl ester compared to other alkyl esters with respect to the alkylation ability of the corresponding malate has been reported: Dugger, R. W.; Ralbovsky, J. L.; Bryant, D.; Commander, J.; Massett, S. S.; Sage, N. A.; Selvidio, J. R. *Tetrahedron Lett.* **1992**, *45*, 6763−6766.

(26) Seebach, D.; Aebi, J.; Wasmuth, D. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, pp 153−159.

(27) Norman, B. H.; Morris, M. L. *Tetrahedron Lett.* **1992**, *45*, 6803−6806.

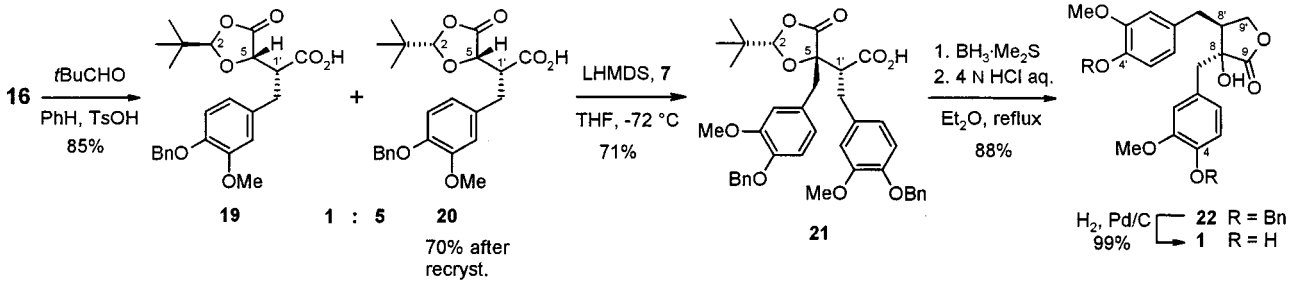
(28) No deuterated diisopropyl malate **13** was obtained after the reaction was quenched at −75 °C using DCl in $D_2O$, indicating that the reaction rate for the enolization of **13** is low at −75 °C, whereas alkylation of the enolate proceeds at that temperature.

(29) Recent example: Yamauchi, S.; Machi, M.; Kinoshita, Y. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 1453−1462.

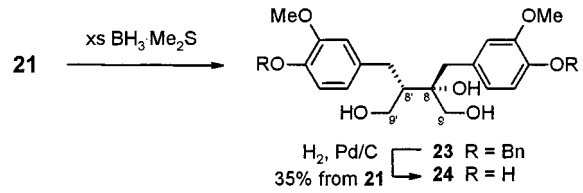
(30) A reversed selectivity was also reported in the condensation reaction between malate enolate and imines, when HMPA was added to the lithium enolate (Ha, D.-C.; Yun, K.-S.; Park, H.-S.; Choung, W.-K.; Kwon, Y.-E. *Tetrahedron Lett.* **1995**, *46*, 8445−8448). On the other hand, no influence on the stereochemical outcome was observed if lithium enolates of malates were alkylated in the presence of HMPA (Grossen, P.; Herold, P.; Mohr, P.; Tamm, C. *Helv. Chim. Acta* **1986**, *67*, 1625−1629).

(31) Gabrielsen, M. V. *Acta Chem. Scand. A* **1975**, *29*, 7−13. In contrast, Seebach et al. reported a 3:2 mixture of diastereoisomers (*cis*- and *trans*-**3**) when the reaction was performed in benzene.[14]

**Scheme 10**




**Scheme 11**




enolate was readily alkylated at that temperature within 5 h, providing dioxolanone **21** as a single isomer in 71% yield. The relative configuration of isomer **21** was determined after its conversion to lactone **22** because spectroscopic data for both diastereomers have been reported in the literature.[10] This transformation (**21** → **22**) was accomplished by reduction of the carboxyl group using 1 equiv of borane dimethyl sulfide complex, followed by treatment of the reaction product with aqueous 4 M HCl, providing **22** in 88% yield (Scheme 10).

The exact equivalence of borane and substrate was crucial because excess of reductant produced the triol **23**, which afforded after hydrogenolytic cleavage of the benzyl ether pentol **24**, carinol,[5b,32] in 35% yield (Scheme 11). Finally, hydrogenolysis of the benzyl ethers of **22** afforded (−)-wikstromol (**1**) as an amorphous solid in quantitative yield.

The $^1$H and $^{13}$C NMR data of lactone **22** and (−)-**1** were in excellent agreement with those reported for the butyrolactone having both benzyl substituents in the "*trans*"-position.[10] Many different values for the optical rotation of (+)- or (−)-**1** were reported in the literature. For (−)-**1** the values range from −15 to −72°.[9] The optical rotation of our material is −39°, which is close to that reported by Brown et al.[9] (−32°).

## Conclusion

We have reported the total synthesis of (−)-wikstromol (**1**), starting from (−)-malic acid (**2**). Using a consecutive alkylation strategy, (−)-**1** was obtained in 30% overall yield, requiring only six synthetic steps from commercially available malic acid ester. This is the shortest and most efficient synthesis of (−)-**1** reported so far.

A second approach from **2**, using the double alkylation of a chiral dienolate as key step, was not successful. All attempts to obtain a chiral dienolate from dioxolanones **4** or **5** failed. Instead of a dienolate, aldol reaction products **8** and **9** were isolated with good stereoselectivities from **4** and **5**, respectively. The configuration of the isomer **9** (2*S*,5*R*,1′*R*) was determined by X-ray structure analysis. The configuration of spirolactone **8** was assigned by analogy to that of **9** to be 2*S*,5*R*,1′*R*. It was reported that the aldol reaction of dioxolanone **3** with pivalaldehyde produced the spirolactone **11** (1′*S*-epimer of **8**), although both the fragmentation of **4** and the aldol reaction of **3** should give the same aldol product.[14] Repetition of the aldol reaction revealed that lactone **8** was always produced as the major isomer, although less selectively than by fragmentation of **4**. Additionally, a third stereoisomer, **12**, was formed, but its relative configuration was not determined.

Since both enantiomers of malic acid esters are available, our methodology provides access to a wide range of other natural α-hydroxylated lactone lignans as well synthetic analogues in very short times. We are currently investigating synthetic routes to other classes of lignans, which will be built up in analogy to the methodology described herein.

## Experimental Section

**General Procedures.** All reactions were performed in dried glassware under an inert ($N_2$) atmosphere. Standard reagents and solvents were purified according to known procedures.[33] Thin layer chromatographic (TLC) analyses were performed on silica gel plates. Column chromatographic purifications ("flash chromatography", FC) were performed as described.[34] All melting points are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were obtained at 300.1 and 75.4 MHz, respectively. Unless otherwise stated, $CDCl_3$ was used as solvent. Infrared (IR) spectra were recorded either from KBr plates or neat. Ultraviolet (UV) spectra were obtained from alcoholic solutions. Mass spectra were achieved by the electron impact (EI) method.

**Preparation of *tert*-Butyl Ester 4.** To a solution of 4.04 g (20 mmol) of dioxolanone **3**[14] in dichloromethane (40 mL) were added 80 mg (0.66 mmol) of DMAP, 14.0 g (189 mmol) of *t*BuOH, 20 mg of *p*TsOH, and 4.33 g (21 mmol) of DCC at 0 °C. The resulting pale yellow suspension was stirred until the reaction was complete (approximately 24 h, monitored by TLC). The reaction mixture was diluted with 100 mL of light petroleum ether, and the white solid was filtered off. The solvent was removed under reduced pressure, and the residue was purified by FC (5 × 18 cm, 10−20% EtOAc/light petroleum ether) to afford *tert*-butyl ester **4**[15] as a white solid (4.93 g, 95%). $^1$H NMR: $\delta$ 5.17 (d, $J$ = 1.0 Hz, 1H, H-2); 4.63 (ddd, $J$ = 7.6, 3.8, 1.0 Hz, 1H, H-5); 2.85 (dd, $J$ = 16.7, 3.8 Hz, 1H, H-1′); 2.65 (dd, $J$ = 16.7, 7.7 Hz, 1H, H-1′); 1.47 (s, 9H, $CO_2t$Bu); 0.98 (s, 9H, *t*Bu). $^{13}$C NMR: $\delta$ 172.56 (s), 168.19 (s), 109.64 (d), 81.79 (s), 71.88 (d), 36.83 (t), 34.20 (s), 27.99 (q), 23.43 (q). Other analytical data were in accordance with those reported by Bartlett et al.[15]

**Preparation of Dimethylamide 5.** A suspension of 2.02 g (10 mmol) of dioxolanone **3**[14] in toluene (50 mL), containing

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(33) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd edition; Pergamon Press: Oxford, 1988.

(34) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(35) ORTEP3 for Windows: Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.

two drops of DMF, was treated with 1.05 mL (1.52 g, 12 mmol) oxalyl chloride at 0 °C. The solid disappeared slowly at room temperature, and a clear, greenish solution was obtained after about 4 h. The solvent and excess of oxalyl chloride were removed in vacuo. The remaining oily acid chloride **6** was dissolved in THF (30 mL), the solution cooled to 0 °C, and 12 mL (24 mmol) of a 2.0 M solution of dimethylamine in THF was added. The reaction mixture was stirred at room temperature for 3 h and then poured into a saturated aqueous $NH_4Cl$ solution (20 mL). The aqueous layer was extracted with $Et_2O$ (2 × 10 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvents were removed under reduced pressure and the remaining solid recrystallized from EtOAc/light petroleum ether, providing 2.05 g (90%) of dimethylamide **5** as white needles. The mother liquor was concentrated and the residue was purified by FC, affording an additional 0.19 g (8%) of **5** as a white solid. Mp: 86−87 °C. $[\alpha]^{25}_D$ −6.5 (*c* 1.02, $CH_2Cl_2$). IR (KBr) *ν* 2960, 1803, 1652, 1196 $cm^{-1}$. $^1H$ NMR: *δ* 5.20 (d, *J* = 0.9 Hz, 1H, H-2); 4.89 (ddd, *J* = 8.2, 2.7, 0.9 Hz, 1H, H-5); 3.04 (s, 3H, Me); 3.00 (s, 3H, Me); 2.92 (dd, *J* = 16.6, 2.7 Hz, 1H, H-1′); 2.74 (dd, *J* = 16.6, 8.2 Hz, 1H, H-1′); 0.98 (s, 9H, *t*Bu). $^{13}C$ NMR: *δ* 173.40 (s), 167.96 (s), 109.56 (d), 72.13 (d), 37.01 (q), 35.56 (q), 34.86 (t), 34.06 (s), 23.41 (q). MS *m*/*z* (%) 230 (58), 172 (35), 126 (33), 116 (28), 87 (84), 72 (100).

**Preparation of Spirolactone 8.** To a cold (−78 °C) solution of 129 mg (0.50 mmol) of dioxolanone **4** in THF (10 mL) was added 1.05 mL (1.1 mmol) of LHMDS (1.06 M in THF) dropwise (internal temperature below −75 °C). After 20 min all starting material was consumed and the pale orange reaction mixture was quenched with 20% DCl in $D_2O$ (0.2 mL). The solution was poured into brine (10 mL) and the aqueous layer extracted with $Et_2O$ (2 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvents were removed under reduced pressure. The crude product was purified by FC (2 × 14 cm, 15% EtOAc/light petroleum ether), affording 27 mg (20%) spirolactone **8** (diastereoselectivity **8**:**11** = 97:3) as a white solid. Mp: 127−129 °C [lit.[14] mp 129 °C]. $[\alpha]^{28}_D$ +33.8 (*c* 0.35, $CH_2Cl_2$) [lit.[14] −31 for the enantiomer (!)]. IR (neat): *ν* 3433, 1801, 1784, 1199 $cm^{-1}$. $^1H$ NMR: *δ* 5.34 (s, 1H, H-2); 4.29 (s, 1H, H-6); 3.14/2.79 (AB, *J* = 17.7 Hz, 2H, H-9); 1.08 (s, 9H, *t*Bu); 0.97 (s, 9H, *t*Bu). $^{13}C$ NMR: *δ* 171.71 (s), 171.21 (s), 110.18 (d), 90.34 (d), 83.23 (s), 42.63 (t), 35.18 (s), 34.07 (s), 26.09 (q), 23.20 (q). MS *m*/*z* (%) 271 (4), 184 (8), 156 (37), 128 (19), 87 (19), 57 (100), 41 (48).

Alternatively, spirolactone **8** was prepared as described previously,[14] along with two other isomers **11** and **12**, in ratios of (**8**:**11**:**12**) 5:1:1 (LDA) or 5:2:1 (LHMDS).

**11**. $^1H$ NMR: *δ* 5.17 (s, 1H, H-2); 4.29 (s, 1H, H-6); 3.15/2.70 (AB *J* = 18.3 Hz, 2H, H-9); 1.03 (s, 9H, *t*Bu); 0.94 (s, 9H, *t*Bu). $^{13}C$ NMR: *δ* 171.84 (s), 107.73 (d), 94.15 (d), 82.65 (s), 39.18 (t), 34.20 (s), 34.06 (s), 25.23 (q).

**12**. $^1H$ NMR: *δ* 5.02 (s, 1H, H-2); 4.46 (s, 1H, H-6); 2.90/2.85 (AB *J* = 17.6 Hz, 2H, H-9); 1.09 (s, 9H, *t*Bu); 1.05 (s, 9H, *t*Bu). $^{13}C$ NMR: *δ* 171.32 (s), 171.29 (s), 108.66 (d), 88.91 (d), 83.70 (s), 37.37 (t), 34.19 (s), 33.90 (s), 25.77 (q), 24.09 (q). MS *m*/*z* (%) 271 (3), 213 (3), 185 (8), 184 (8), 156 (12), 87 (12), 57 (100), 41 (29).

**Preparation of Dimethylamide 9.** To a cold (−78 °C) solution of 115 mg (0.50 mmol) of dioxolanone **5** in THF (10 mL) was added 1.05 mL (1.1 mmol) of LHMDS (1.06 M in THF) dropwise (internal temperature below −75 °C). After 30 min, all starting material was consumed (TLC) and the reaction mixture was quenched with 20% DCl in $D_2O$ (0.2 mL). Brine (10 mL) was added, and the aqueous layer was extracted with $Et_2O$ (2 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvents were removed in vacuo. The crude product was purified by FC (2 × 14 cm, 10−20% EtOAc/light petroleum ether), affording 60 mg (38%) of dimethylamide **9** and 5 mg (3%) of its epimer (ratio 12:1) as white solids. Mp: 112−114 °C. $[\alpha]^{30}_D$ +10.6 (*c* 1.13, $CH_2Cl_2$). IR (neat): *ν* 3434, 1795, 1648, 1190, 1149, 1063 $cm^{-1}$. $^1H$ NMR: *δ* 5.24 (s, 1H, H-2); 4.20 (br s, 1H, OH); 3.62 (s, 1H, H-6); 3.14/2.98 (AB *J* = 15.5 Hz, 2H, H-9); 3.01 (s, 3H, Me); 2.96 (s, 3H, Me); 1.07 (s, 9H, *t*Bu); 0.98 (s, 9H, *t*Bu). $^{13}C$ NMR: *δ* 175.31 (s), 168.32 (s), 108.73 (d), 82.90 (s), 76.02 (d), 37.77 (q), 36.50 (t), 36.06 (s), 35.74 (q), 34.48 (s), 27.54 (q), 23.64 (q). MS *m*/*z* (%) 316 (7), 258 (8), 229 (18), 173 (18), 87 (100), 72 (54).

***epi*-9.** $^1H$ NMR: *δ* 5.37 (s, 1H, H-2); 3.72 (s, 1H, H-6); 3.21/2.75 (AB *J* = 15.3 Hz, 2H, H-9); 3.02 (s, 3H, Me); 2.91 (s, 3H, Me); 2.60 (br s, 1H, OH); 1.12 (s, 9H, *t*Bu); 0.95 (s, 9H, *t*Bu). MS *m*/*z* (%) 316 (4), 173 (26), 117 (34), 87 (57), 72 (100).

**Preparation of Diisopropyl Malate 14.** A solution of 1.60 g (7.34 mmol) of malate **13** and 2.99 g (9.72 mmol) of benzyl bromide **7** in THF (50 mL) was cooled to −76 °C (internal temperature). Then 15 mL (15.9 mmol) of a 1.06 M solution of LHMDS in THF was added (internal temperature below −73 °C). The reaction mixture was warmed to +8 °C within 12 h; at this time, the reaction was determined to be complete as monitored by TLC. The reaction was quenched by the addition of a saturated aqueous $NH_4Cl$ solution (20 mL) and acidified (pH ∼ 1−2) using an 1 M aqueous HCl solution. The aqueous layer was extracted with $Et_2O$ (3 × 15 mL), and the combined organic phases dried over $MgSO_4$. The solid was filtered off, and the solvents were removed under reduced pressure. The crude product was purified by FC (4 × 25 cm, 25−60% EtOAc/light petroleum ether) to afford 2.64 g of malate **14** (80%) as pale yellow oil. $[\alpha]^{24}_D$ +12.2 (*c* 1.68, $CH_2Cl_2$). IR (neat): *ν* 3500, 1733, 1263, 1107 $cm^{-1}$. $^1H$ NMR: *δ* 7.45−7.25 (m, 5H, H-arom); 6.82 (d, *J* = 1.8 Hz, 1H, H-2′); 6.82 (d, *J* = 8.1 Hz, 1H, H-5′); 6.74 (dd, *J* = 8.1, 1.8 Hz, 1H, H-6′); 5.13 (s, 2H, O−C$H_2$-aryl); 5.08 (sept, *J* = 6.2 Hz, 1H, O−C$H$(C$H_3$)$_2$); 4.99 (sept, *J* = 6.2 Hz, 1H, O−C$H$(C$H_3$)$_2$); 4.06 (br s, 1H, H-2); 3.88 (s, 3H, OMe); 3.25 (br s, 1H, OH); 3.14−3.03 (m, 2H, H-3, C$H_2$-aryl); 2.90 (m, 1H, C$H_2$-aryl); 1.27 (d, *J* = 6.2 Hz, 3H, CH(C$H_3$)$_2$); 1.25 (d, *J* = 6.2 Hz, 3H, CH(C$H_3$)$_2$); 1.20 (d, *J* = 6.2 Hz, 3H, CH-(C$H_3$)$_2$); 1.16 (d, *J* = 6.2 Hz, 3H, CH(C$H_3$)$_2$). $^{13}C$ NMR: *δ* 173.11 (s), 171.68 (s), 149.60 (s), 146.87 (s), 137.25 (s), 131.64 (s), 128.47 (d), 127.75 (d), 127.24 (d), 121.29 (d), 114.20 (d), 113.03 (d), 71.10 (t), 69.73 (d), 69.69 (d), 68.55 (d), 55.99 (q), 50.18 (d), 33.65 (t), 21.66 (q). MS *m*/*z* (%) 444 (100), 402 (9), 385 (20), 269 (26), 207 (35), 91 (33). Anal. Calcd for $C_{25}H_{32}O_7$: C 67.55, H 7.26. Found: C 67.66, H 7.21.

**Preparation of Diacid 16.** Diisopropyl ester **14** (3.00 g, 6.75 mmol) was dissolved in a 1 M ethanolic KOH solution (30 mL). The pale yellow solution was stirred for 72 h at room temperature, during which a white precipitate formed. EtOH was removed under reduced pressure, and the residue was dissolved in water (50 mL). $Et_2O$ (50 mL) was added. The aqueous layer was acidified with a 2 M aqueous HCl solution and saturated with solid NaCl. The aqueous solution was extracted with $Et_2O$ (3 × 50 mL) and the combined organic extracts were dried over $MgSO_4$. After filtration and removal of the solvent in vacuo, diacid **16** was obtained in quantitative yield. The crude material was recrystallized from $CHCl_3$ containing small amounts of MeOH to afford diastereoisomerically pure **16** (2.16 g, 87%) as a white solid. Mp: 153−154 °C. $[\alpha]^{25}_D$ −4.2 (*c* 0.56, MeOH). IR (KBr): *ν* 3450−2300, 1740, 1690, 1267 $cm^{-1}$. $^1H$ NMR ($CD_3OD$): *δ* 7.44−7.25 (m, 5H, H-arom); 6.89 (d, *J* = 8.1 Hz, 1H, H-5′); 6.89 (d, *J* = 1.7 Hz, 1H, H-2′); 6.75 (dd, *J* = 8.1, 1.7 Hz, 1H, H-6′); 5.04 (s, 2H, O−C$H_2$-aryl); 4.95 (br s, 3H, OH, $CO_2H$); 4.12 (d, *J* = 4.1 Hz, 1H, H-2); 3.83 (s, 3H, OMe); 3.14 (ddd, *J* = 8.2, 7.2, 4.1 Hz, 1H, H-3); 3.04 (dd, *J* = 13.6, 7.2 Hz, 1H, C$H_2$-aryl); 2.85 (dd, *J* = 13.6, 8.2 Hz, 1H, C$H_2$-aryl). $^{13}C$ NMR ($CD_3OD$): *δ* 177.05 (s), 176.09 (s), 151.64 (s), 148.64 (s), 139.31 (s), 134.44 (s), 129.91 (d), 129.34 (d), 129.22 (d), 122.93 (d), 116.51 (d), 114.98 (d), 72.91 (t), 71.68 (d), 56.97 (q), 52.64 (d), 35.07 (t). MS *m*/*z* (%) 361 (100), 343 (29), 342 (30), 324 (29), 228 (14), 181 (13). Anal. Calcd for $C_{19}H_{20}O_7$: C 63.33, H 5.59. Found: C 63.13, H 5.66.

**Preparation of Dioxolanone 20.** Recrystallized, dry TsOH (100 mg) and 2 mL (1.57 g, 18 mmol) of pivalaldehyde were added to a suspension of 1.80 g (5.00 mmol) of diacid **16** in benzene (100 mL). The suspension was refluxed for 8 h using a Soxhlet apparatus, filled with activated 4 Å molecular sieves. After 4 h, additional pivalaldehyde (2 mL) was added, and the refluxing was continued until all starting material had been consumed. Benzene and excess pivalaldehyde were

removed under reduced pressure, and the products **19** and **20** were separated from TsOH by FC (3 × 16 cm, 60% EtOAc/light petroleum ether, containing 0.5% AcOH). Recrystallization from EtOH/water afforded diastereoisomerically pure **20** (1.50 g, 70%) as a white solid. Mp: 125−126 °C. $[\alpha]^{25}_D$ −29.5 (*c* 0.82, $CH_2Cl_2$). IR (KBr): *ν* 3280, 1799, 1732, 1263, 1222 $cm^{-1}$. $^1H$ NMR: *δ* 7.45−7.25 (m, 5H, H-arom); 6.81 (d, *J* = 8.1 Hz, 1H, H-5″); 6.76 (d, *J* = 1.5 Hz, 1H, H-2″); 6.69 (dd, *J* = 8.1, 1.5 Hz, 1H, H-6″); 5.13 (s, 2H, O−C*H*$_2$-aryl); 5.09 (s, 1H, H-2); 4.21 (d, *J* = 2.8 Hz, 1H, H-5); 3.87 (s, 3H, OMe); 3.25−3.18 (m, 2H, H-1′, C*H*$_2$-aryl); 2.95 (dd, *J* = 15.6, 11.1 Hz, 1H, C*H*$_2$-aryl); 0.97 (s, 9H, *t*Bu). $^{13}C$ NMR: *δ* 175.77 (s), 172.18 (s), 149.74 (s), 147.15 (s), 137.10 (s), 130.36 (s), 128.51 (d), 127.80 (d), 127.22 (d), 121.16 (d), 114.20 (d), 112.71 (d), 109.61 (d), 73.65 (d), 71.06 (t), 55.96 (q), 47.41 (d), 34.26 (s), 33.02 (t), 23.54 (q). MS *m*/*z* (%) 428 (55), 343 (10), 314 (7), 297 (20), 251 (100), 228 (7). Anal. Calcd for $C_{24}H_{28}O_7 \cdot {}^1/_2H_2O$: C 65.89, H 6.68. Found: C 66.13, H 6.62.

**Preparation of Dioxolanone 21.** A solution of 1.00 g (2.33 mmol) of dioxolanone **20** and 0.92 g (3.00 mmol) of benzyl bromide **7** in THF (20 mL) was cooled to −77 °C. Then 4.7 mL (5.0 mmol) of a 1.06 M solution of LHMDS in THF (internal temperature below −72 °C) was added. The resulting pale orange solution was stirred for 5 h at −75 °C and quenched with a saturated aqueous $NH_4Cl$ solution (20 mL). The aqueous layer was acidified (pH ∼ 2) using a 2 M aqueous HCl solution and was extracted with $Et_2O$ (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvents were removed in vacuo. FC of the residue (4 × 23 cm, 30−70% EtOAc/hexane) and recrystallization from EtOH/water provided 1.08 g (71%) of dioxolanone **21** as a pale yellow solid. Mp: 72−74 °C. $[\alpha]^{22}_D$ +2.9 (*c* 0.73, $CH_2Cl_2$). IR (KBr): *ν* 3400−2500, 1788, 1739, 1713, 1264 $cm^{-1}$. $^1H$ NMR: *δ* 7.45−7.25 (m, 10H, H-arom); 6.81 (d, *J* = 8.1 Hz, 1H, H-5″); 6.80 (br s, 1H, H-2″); 6.78 (d, *J* = 8.1 Hz, 1H, H-5‴); 6.73 (br d, *J* = 8.1 Hz, 1H, H-6″); 6.72 (br s, 1H, H-2‴); 6.67 (br d, *J* = 8.1 Hz, 1H, H-6‴); 5.13 (s, 2H, O−C*H*$_2$-aryl); 5.08 (s, 2H, O−C*H*$_2$-aryl); 4.04 (s, 1H, H-2); 3.85 (s, 3H, OMe); 3.81 (s, 3H, OMe); 3.44 (d, *J* = 13.7 Hz, 1H, C*H*$_2$-aryl); 3.41 (br d, *J* = 11 Hz, 1H, H-1′); 3.12 (d, *J* = 13.7 Hz, 1H, C*H*$_2$-aryl); 3.08 (br d, *J* = 13 Hz, 1H, C*H*$_2$-aryl); 2.97 (dd, *J* = 13, 11 Hz, 1H, C*H*$_2$-aryl); 0.80 (s, 9H, *t*Bu). $^{13}C$ NMR: *δ* 175.89 (s), 173.84 (s), 149.62 (s), 149.58 (s), 147.51 (s), 147.04 (s), 137.11 (s), 136.83 (s), 130.98 (s), 128.50 (d), 128.46 (d), 127.85 (d), 127.76 (d), 127.24 (d), 126.85 (s), 122.60 (d), 120.66 (d), 114.09 (d), 113.99 (d), 112.54 (d), 110.04 (d), 82.53 (s), 70.98 (t), 70.91 (t), 55.95 (q), 55.89 (q), 54.66 (d), 37.64 (s), 34.44 (t), 32.67 (s), 23.19 (q). MS *m*/*z* (%) 655 (25), 654 (24), 568 (15), 317 (79), 227 (100). Anal. Calcd for $C_{39}H_{42}O_9 \cdot {}^1/_2H_2O$: C 70.57, H 6.53. Found: C 70.19, H 6.44.

**Preparation of Lactone 22.** To a solution of 0.90 g (1.37 mmol) of dioxolanone **21** in $Et_2O$ (40 mL) was added 0.14 mL (1.4 mmol) of borane dimethyl sulfide complex dropwise at room temperature. The solution was heated under reflux for 5 h until all starting material had been consumed (monitored by TLC). The reaction mixture was cooled to 10 °C, and a 4 M aqueous HCl solution (10 mL) was added very carefully (!). The biphasic system was heated under reflux for additional 3 h until complete conversion to lactone **22** occurred (monitored by TLC). The acid was diluted with water (30 mL) after cooling to room temperature. The aqueous layer was extracted with $Et_2O$ (3 × 10 mL), the combined organic phases were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. FC of the residue (3 × 20 cm, 25−50% EtOAc/light petroleum ether) afforded 0.67 g (88%) of lactone **22** as a colorless amorphous solid. $[\alpha]^{25}_D$ −19.6 (*c* 0.84, $CH_2Cl_2$). IR (KBr): *ν* 3457, 1768, 1264, 1228 $cm^{-1}$. $^1H$ NMR: *δ* 7.43−7.23 (m, 10H, H-arom); 6.76 (d, *J* = 8.1 Hz, 1H, H-5′); 6.76 (d, *J* = 8.1 Hz, 1H, H-5); 6.75 (d, *J* = 1.7 Hz 1H, H-2′); 6.63 (d, *J* = 1.7 Hz, 1H, H-2); 6.58 (dd, *J* = 8.1, 1.7 Hz, 1H, H-6′); 6.57 (dd, *J* = 8.1, 1.7 Hz, 1H, H-6); 5.10 (s, 2H, O−C*H*$_2$-aryl); 5.09 (s, 2H, O−C*H*$_2$-aryl); 4.01 (dd, *J* = 9.1, 6.7 Hz, 1H, H-9′); 3.95 (dd, *J* = 8.8, 6.6 Hz, 1H, H-9′); 3.81 (s, 3H, OMe); 3.80 (s, 3H, OMe); 3.11 (s, 1H, OH); 3.10 (d, *J* = 13.7 Hz, 1H, H-7); 2.90 (d, *J* = 13.7 Hz, 1H, H-7); 2.88 (m, 1H, H-8′); 2.54−2.43 (m, 2H, H-7′). $^{13}C$ NMR: *δ* 178.46 (s), 149.66 (s), 149.50 (s), 147.40 (s), 146.78 (s), 137.04 (s), 136.94 (s), 131.59 (s), 128.41 (d), 127.73 (d), 127.37 (s), 127.14 (d), 122.34 (d), 120.69 (d), 114.28 (d), 113.87 (d), 112.72 (d), 76.30 (s), 71.02 (t), 70.92 (t), 70.12 (t), 55.89 (q), 43.54 (d), 41.76 (t), 31.38 (t). MS *m*/*z* (%) 554 (50), 317 (61), 227 (100).

**Preparation of (−)-Wikstromol (1).** Lactone **22** (0.44 g, 0.79 mmol) was dissolved in degassed EtOH (30 mL) at room temperature. Palladium (10% on charcoal, 80 mg) was added, and the mixture was exposed to a $H_2$ atmosphere for 20 h. The suspension was filtered over Celite and the filtrate concentrated in vacuo. The residue was purified by FC (2 × 22 cm, 50−70% EtOAc/light petroleum ether) to afford 0.29 g (98%) of (−)-wikstromol **1** as an amorphous solid. $[\alpha]^{25}_D$ −39.2 (*c* 0.95, $CH_2Cl_2$). IR (KBr): $\tilde{\nu}$ 3428, 1764, 1272 $cm^{-1}$. $^1H$ NMR: *δ* 6.83 (d, *J* = 8.1 Hz, 2H, H-5, H-5′); 6.70 (d, *J* = 1.7 Hz 1H, H-2); 6.63 (dd, *J* = 8.1, 1.7 Hz, 1H, H-6); 6.63−6.59 (m, 2H, H-2′, H-6′); 5.80 (br s, 2H, OH); 4.04 (dd, *J* = 9.1, 6.7 Hz, 1H, H-9′); 3.99 (dd, *J* = 8.8, 6.6 Hz, 1H, H-9′); 3.83 (s, 3H, OMe); 3.81 (s, 3H, OMe); 3.30 (br s, 1H, OH); 3.13 (d, *J* = 13.7 Hz, 1H, H-7); 2.93 (d, *J* = 13.7 Hz, 1H, H-7); 2.91 (m, 1H, H-8′); 2.56−2.46 (m, 2H, H-7′). $^{13}C$ NMR: *δ* 178.72 (s), 146.57 (s), 146.53 (s), 144.83 (s), 144.16 (s), 130.32 (s), 126.19 (s), 123.05 (d), 121.35 (d), 114.52 (d), 114.31 (d), 112.76 (d), 111.51 (d), 76.44 (s), 70.26 (t), 55.87 (q), 55.83 (q), 43.65 (d), 41.78 (t), 31.43 (t). MS *m*/*z* (%) 374 (7), 137 (100), 122 (4).

**Acknowledgment.** The author is indebted to Professor M. G. Peter for his generous support and continuous interest in this research. Thanks to Dr. D. Schanzenbach for many critical discussions and to Dr. U. Schilde for the X-ray crystal structure analysis of compound **9**. Financial support by the Deutsche Forschungsgemeinschaft (Se 875/1-1) and by the Fonds der Chemischen Industrie is gratefully acknowledged.

**Supporting Information Available:** $^1H$ NMR and $^{13}C$ NMR spectra of compounds **4**, **5**, **8**, **9**, **12**, and a mixture of **8** and **11**, $^1H$ NMR spectra of crude **8**/**11**/**12** and of *epi*-**9**, and $^{13}C$ NMR spectra of **22** and **1**. Tables of X-ray structural data for compound **9.** This material is available free of charge via the Internet at http://pubs.acs.org.

JO001547Z