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Enantioselective Synthesis of (+)-Obolactone Based on a Symmetry-Breaking Wacker Monooxidation of a Diene

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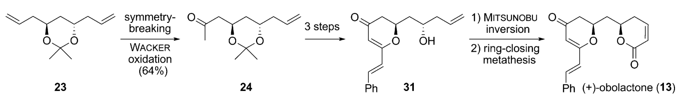
ABSTRACT

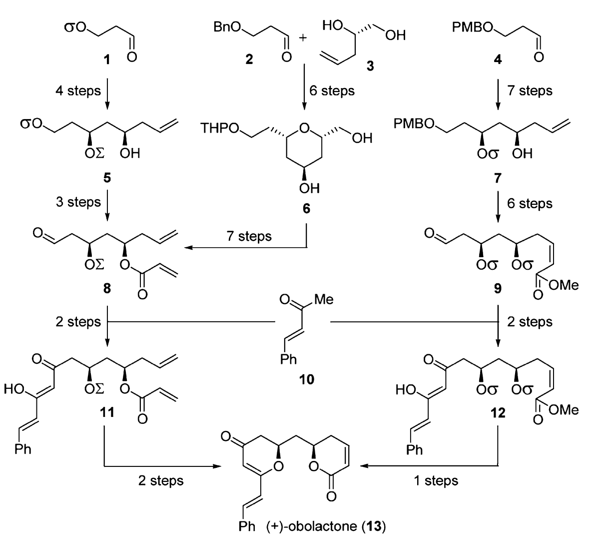


A concise synthesis of the dihydro-α-pyrone/dihydro-γ-pyrone natural product (+)-obolactone (13) is disclosed. The dienediol acetonide 23 (≥97% ee) was obtained from 1,5-dichloropentane-2,4-dione in four steps. A Wacker monooxidation of 23 furnished the monoketone 24 in 64% yield. The OH group of the ensuing dihydro-γ-pyrone 31 was esterified under Mitsunobu conditions with cinnamic acid (→ 80% inversion and 20% retention of configuration). A ring-closing metathesis formed the dihydro-α-pyrone moiety of the target in the terminating step.

Ten years ago, a Gif-sur-Yvette team isolated the title compound (**13**) from the trunk bark of a tropical tree (*Cryptocarya obovata* R. Br.) indigenous to northern Vietnam.[1] Obolactone acts against nasopharyngeal carcinoma KB cells (IC_{50} = 3 μM) and against *Trypanosoma brucei brucei*, which causes African sleeping sickness (IC_{50} = 5.3 μM).[2] The asymmetric unit of crystalline **13** (mp 116 °C) contained four distinct conformers according to an X-ray analysis.[1] The latter revealed two stereocenters, either *R*,*R* or *S*,*S* configured, one dihydro-α-pyrone ring, and one dihydro-γ-pyrone moiety.[1] The CD spectrum showed that the correct assignment was *R*,*R*.[1]

She et al. reported the first total synthesis of (+)-obolactone (11 steps).[3] Total syntheses by Shabita et al. (17 steps)[4] and Krishna et al. (16 steps)[5] followed.

Scheme 1. Previous Total Syntheses[3−5] of (+)-Obolactone (**13**)[a]



[a] Σ = TBDPS = *tert*-butyldiphenylsilyl; σ = TBS = *tert*-butyldimethylsilyl; Bn = benzyl; PMB = *p*-methoxybenzyl; THP = tetrahydropyran-2-yl.

As Scheme 1 summarizes all approaches aimed at *syn*-1,3-diol monoethers first, i.e., the silyl ether **5**, the tetrahydropyran **6**, and the silyl ether **7**. Another common

(1) Dumontet, V.; Hung, N. V.; Adeline, M.-T.; Riche, C.; Chiaroni, A.; Sévenet, T.; Guéritte, F. *J. Nat. Prod.* **2004**, *67*, 858–862.
(2) Davis, R. A.; Sykes, M. L.; Avery, V. M.; Suraweera, L.; Fechner, G. A.; Quinn, R. J.; Demirkiran, O. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4057–4059.
(3) Zhang, J.; Li, Y.; Wang, W.; She, X.; Pan, X. *J. Org. Chem.* **2006**, *71*, 2918–2921.
(4) Sabitha, G.; Prasad, M. N.; Shankaraiah, K.; Yadav, J. S. *Synthesis* **2010**, *7*, 1171–1175.
(5) Steps 1−4: Wu, Y.; Esser, L.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 4308–4310. Wu, Y.; Esser, L.; De Brabander, J. K. *Angew. Chem.* **2000**, *112*, 4478–4480. Steps 5−16: Krishna, P. R.; Srinivas, P. *Tetrahedron Lett.* **2010**, *51*, 2295–2296.

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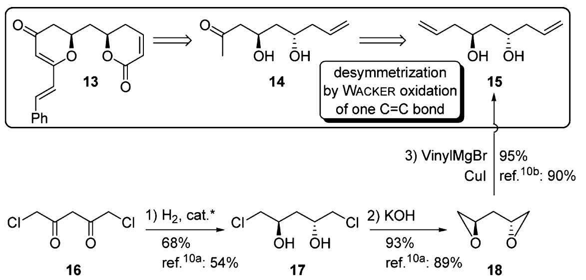
feature was the use of styryl methyl ketone (**10**) for introducing the phenyl ring and establishing the dihydro-γ-pyrone moiety thereafter. The dihydro-α-pyrone stemmed either from a ring-closing metathesis of acrylate **11**[3,4] or from the lactonization of the silylated seco-ester **12**.[5]

Scheme 2. Retrosynthetic Analysis of (+)-Obolactone (**13**). Identifying the *Anti*-Configured 1,3-Diol **15** as a Precursor and Preparing it via a Three-Step Route[10] Rather than by a One-Step Access[12]

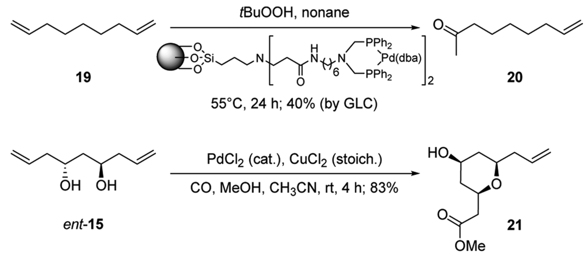


cat.* = $[Me_2NH_2]^{\oplus}[RuCl(S\text{-BINAP})]_2(\mu\text{-}Cl)_3{}^{\ominus}$

In our retrosynthetic analysis (Scheme 2, top row), (+)-obolactone (**13**) was traced back to an *anti*-configured 1,3-diol, namely compound **14**. The latter also represents a methyl ketone. This feature suggested that it might be accessible from a Wacker oxidation.[6] Ideally, the latter would act on the *anti*-configured dienediol **15**. The challenge in transforming **15** into **14** was to oxidize one C=C bond while leaving the other C=C bond intact. This defined the key step of our approach. Converting *anti*-diol **14** into target **13** would entail cinnamoylation, dihydro-γ-pyrone formation with retention of configuration, acryloylation with inversion of configuration, and dihydro-α-pyrone formation by metathesis.

The desired Wacker monooxidation of nona-1,8-dienediol **15** had little literature precedence (Scheme 3). The monooxidation of the parent diene **19** succeeded in 40% yield[7] under nonclassical[8] conditions. In a Wacker-type etherification/methoxycarbonylation, nona-1,8-dienediol *ent*-**15** gave the THP-containing methyl ester **21** in twice the yield.[9] This gradation is plausible expecting that **20** should be as susceptible as **19** to C=C oxidation whereas **21**, due to an increase of ring strain, should not.

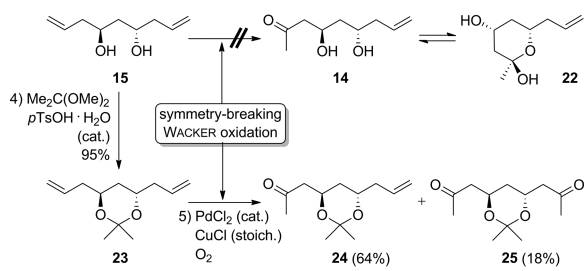
Scheme 3. Modified Wacker Monooxidation of Nona-1,8-diene **19**[7] and a Wacker-Type Monooxidation/Methoxycarbonylation of Nona-1,8-dienediol *ent*-**15**[9]



dba = dibenzylideneacetone (1,5-diphenylpenta-1,4-dien-3-one)

Following a three-step sequence by Rychnovsky et al.,[10] the *anti*-configured 1,3-diol **15** was synthesized from 1,5-dichloropentane-2,4-dione (**16**) in 60% overall yield (lit.[10] 51%) and with ≥97% ee[11] (Scheme 2). Krische et al. published an intriguing one-step synthesis of the same 1,3-diol enantiomer **15** from propane-1,3-diol.[12] We reproduced their reaction but abandoned it upon scale-up because of the high costs for the catalyst (5 mol % of $[Ir(cod)Cl]_2$) and the ligand [10 mol % of 2,2′-bis(diphenylphosphino)-5,5′-dichloro-6,6′-dimethoxy-1,1′-biphenyl].

Scheme 4. Nona-1,8-diene-4,6-diol **15** and the Corresponding Acetonide (**23**) in Symmetry-Breaking Wacker Monooxidations



Attempted Wacker monooxidations of the unprotected dienediol **15** under an atmosphere of O_2 in the presence of $PdCl_2$ (10 mol %) and CuCl (1.0 equiv) failed (Scheme 4).[13] They delivered neither the monoketone-containing 1,3-diol **14** nor the corresponding hemiketal **22**. Protecting the hydroxy groups of dienediol **15** with dimethoxypropane provided the acetonide **23** in 95% yield.[14] Under the

(6) Reviews: (a) Henry, P. M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley & Sons: New York, 2002; pp 2119–2139. (b) Takacs, J. M.; Jiang, X.-t. *Curr. Org. Chem.* **2003**, *7*, 369–396. (c) Hintermann, L. In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 379–388. (d) Hintermann, L. In *Handbook of C–H Transformations: Applications in Organic Synthesis*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; pp 287–298. (e) Cornell, C. N.; Sigman, M. S. *Inorg. Chem.* **2007**, *46*, 1903–1909.

(7) Zweni, P. P.; Alper, H. *Adv. Synth. Catal.* **2004**, *346*, 849–854.

(8) Review: Michel, B. W.; Sigman, M. S. *Aldrichimica Acta* **2011**, *44*, 55–62.

(9) Yang, Z.; Zhang, B.; Zhao, G.; Ynag, J.; Xie, X.; She, X. *Org. Lett.* **2011**, *13*, 5916–5919.

(10) (a) Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. *J. Org. Chem.* **1991**, *56*, 5161–5169. (b) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022–3023.

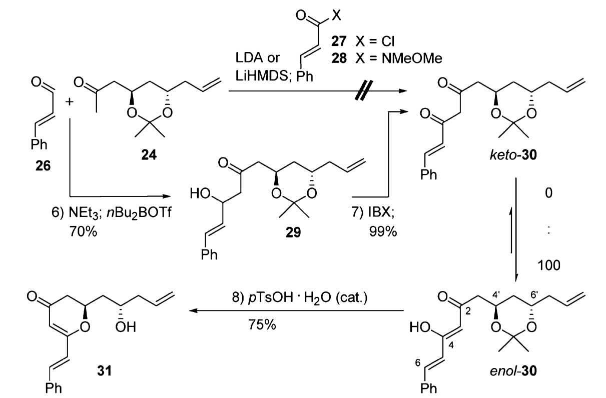
(11) Initially, the enantiopurity of diol **17** was assessed by comparing its specific rotation [$[\alpha]^{20}_D$ = +23.0 (c = 0.88, $CHCl_3$)] to the published value [$[\alpha]^{24}_D$ = +21.1 (c = 1.13, $CHCl_3$)[10a]]. The specific rotation of diol **15** [$[\alpha]^{20}_D$ = +27.7 (c = 0.32, $CHCl_3$)] is missing in refs 10a and 12; $[\alpha]^{24}_D$ = +35.0 (c = 1.00, $CHCl_3$) is published in the Supporting Information of: Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3108–3111. The absolute value of the specific rotation of follow-up product (+)-obolactone (**13**) superceded that of other synthetic specimens[2–4] but lagged that of natural **13**.[1] This led us to believe that our ee was in the upper 90% percentile rank.

(12) Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018–5021. Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem.* **2009**, *121*, 5118–5121.

(13) Procedure: Li, D.-R.; Zhang, D.-H.; Sun, C. Y.; Zhang, J.-W.; Yang, L.; Chen, J.; Liu, B.; Su, C.; Zhou, W.-S.; Lin, G.-Q. *Chem.—Eur. J.* **2006**, *12*, 1185–1204.

previously sketched conditions, this substrate underwent a Wacker monooxidation furnishing the monoketone **24** in 64% yield (Scheme 4). An 18% yield of the undesired diketone **25** resulted as well. These percentages arose after the reaction was monitored by TLC and the reaction mixture worked up when the monoketone was deemed to be the most prominent constituent. Compound **25** eluted later than **24** during purification by column flash chromatography on silica gel.[15]

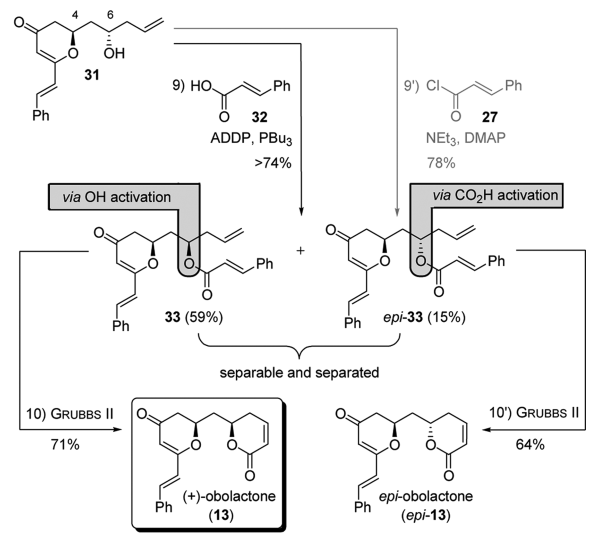
Scheme 5. Elaborating the Wacker Monooxidation Product **24** into the Dihydro-γ-pyranone Moiety of (+)-Obolactone (**13**)



IBX = "2-iodoxybenzoic acid" = commonly used name of a monocyclic isomer of the bicyclic oxidant 1-hydroxy-1λ^3,2-benziodoxol-3(1*H*)-one-1-oxide

In order to establish the dihydro-γ-pyranone moiety of (+)-obolactone (**13**), we had to cinnamoylate the kinetic enolate of monoketone **24** (Scheme 5). However, treatment of **24** with LDA or LiHMDS followed by addition of cinnamoyl chloride (**27**)[16] or of the Weinreb amide **28** of cinnamic acid provided none of the desired diketone *keto*-**30** or a tautomeric enol. We avoided this difficulty by an aldolization/oxidation sequence. The dibutylboron enolate of monoketone **24** formed with the desired regioselectivity upon exposure to 1.1 equiv of both Bu_2BOTf and NEt_3 for 30 min.[17] Addition to cinnamaldehyde (**26**) led to the β-hydroxyketone(s) **29** in 70% yield. Oxidation with IBX[18] rendered the *enol*-**30**[19] of the desired diketone *keto*-**30** (99% yield).[20] The dihydro-γ-pyranone **31** was completed in 75% yield by a pTsOH·H_2O-induced cyclodehydration.

Scheme 6. Converting the Homoallyl Alcohol Moiety of Intermediate **31** into the Dihydro-α-pyranone Moiety of (+)-Obolactone (**13**). Competition between Mitsunobu Inversion (→ **33**) and "Mitsunobu Esterification" (→ *epi*-**33**) in the Cinnamate-Forming Step



ADDP = azodicarboxylic acid dipiperidide; DMAP = 4-(dimethylamino)pyridine

In order to ensure the *syn*-orientation of the C,O bonds in (+)-obolactone (**13**), the *anti*-configured homoallylic alcohol **31** was to be combined with an α,β-unsaturated carboxylic acid under Mitsunobu conditions[21] (Scheme 6, top). The standard inducers PPh_3/DEAD or PPh_3/DIAD

(14) Krische et al. synthesized the acetonide **23** from the 1,3-diol **15**, $Me_2C(OMe)_2$ (15 equiv), and pyridinium p-toluenesulfonate (10 mol %) in CH_2Cl_2 in 91% yield.[12]

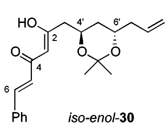
(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(16) Diketone formation from lithium enolates and acyl chlorides has been rarely described, e.g.: (a) Mayweg, A. V. W.; VanDeusen, C.; Wender, P. A. *Org. Lett.* **2003**, *5*, 277–279. (b) Koehler, M. F. T.; Sendzik, M.; Wender, P. A. *Org. Lett.* **2003**, *5*, 4549–4552.

(17) Procedure: Cote, B.; Coleman, P. J.; Connell, B. T.; Evans, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 10893–10898.

(18) Reviews: (a) Zhdankin, V. V. *Curr. Org. Synth.* **2005**, *2*, 121–145. (b) Satam, V.; Harad, A.; Rajule, R.; Pati, H. *Tetrahedron* **2010**, *66*, 7659–7706. (c) Kirsch, S. F.; Duschek, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1524–1552. Kirsch, S. F.; Duschek, A. *Angew. Chem.* **2011**, *123*, 1562–1590.

(19) The isolated enol ($\delta_{C\mathit{H}=C(OH)}$ = 5.70, δ_{OH} = 15.3 ppm; $\delta_{CH=C(OH)}$ = 175.9, $\delta_{CH=C(OH)}$ = 99.6, $\delta_{C=O}$ = 196.7 ppm) possessed structure *enol*-**30** rather than *iso-enol*-**30** because HMBC cross-peaks related 4′-H (δ = 4.31 ppm) to $\delta_{C=O}$ (C-2) and 6-H (δ = 7.60 ppm) to $\delta_{CH=C(OH)}$ (C-4). 6′-H (δ = 3.89 ppm) and these ^{13}C nuclei entertained no cross-peak.



iso-enol-**30**

(20) Procedure: More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001–3003.

(21) Reviews: (a) But, T. Y. S.; Toy, P. H. *Chem. Asian J.* **2007**, *2*, 1340–1355. (b) Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P.; Swamy, K. C. K. *Chem. Rev.* **2009**, *109*, 2551–2651.

(22) ADDP (azodicarboxylic acid dipiperidide) was prepared as described byMakriyannis, A.; Swissman, E. E. *J. Org. Chem.* **1973**, *38*, 1652-1557.

(23) Conditions from Yamamiya, Y.; Kuwamura, Y.; Ito, S.; Tsunoda, T. *Tetrahedron Lett.* **1995**, *36*, 2529–2530. Note that we employed ADDP (ref 22) instead of TMAD (*N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide).

(24) This eluent was found abandoning efforts to separate the mixture of diastereomeric crotonates, which we had obtained from a condensation of the homoallylic alcohol **31** and *trans*-crotonic acid under Mitsunobu conditions. The analogous acrylates did not result under similar conditions.

(25) Grynkiewicz, G. *Rocz. Chem.* **1976**, *50*, 1449–1451.

(26) Farina, V. *Tetrahedron Lett.* **1989**, *30*, 6645–6648.

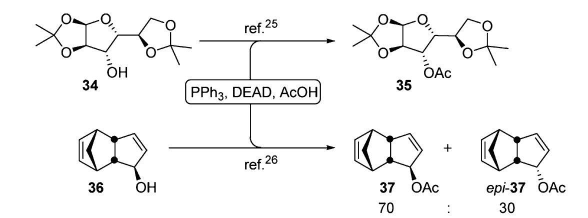
(27) β-Hydroxylactones are amenable to competing OH and CO_2H activations in the presence of PPh_3 and DEAD, too: Brüntrup, G.; Chucholowski, A.; Mulzer, J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 622–623. Brüntrup, G.; Chucholowski, A.; Mulzer, J. *Angew. Chem.* **1979**, *91*, 654–655.

(28) Recent reviews: (a) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746–1787. (b) Majumdar, K. C.; Chattopadhyay, B.; Ray, K. *Curr. Org. Synth.* **2010**, *7*, 153–176. (c) Cossy, J.; Arseniyadis, S.; Meyer, C. *Metathesis in Natural Product Synthesis*; Wiley-VCH: Weinheim, 2010. (d) Prunet, J. *Eur. J. Org. Chem.* **2011**, 3634–3647. (e) Kotha, S.; Dipak, M. K. *Tetrahedron* **2012**, *68*, 397–421.

of such a transformation were unable to join **31** and cinnamic acid (**32**), though. In contrast the combination PBu_3/ADDP[22] gave the desired cinnamate **33** in 59% yield.[23] Surprisingly, the diasteromeric cinnamate *epi*-**33** was obtained, too (15% yield). **33** and *epi*-**33** were separated by flash chromatography on silica gel.[15] Employing toluene/EtOAc as the mobile phase[24] **33** eluted first.

Having a configurationally inverted C–O bond, the major cinnamate **33** must have formed after activation of the OH group of the homoallyl alcohol **31**, the overall reaction being a Mitsunobu inversion. The minor cinnamate *epi*-**33** retained the C–O bond configuration of its predecessor **31** (which became clear when esterification of **31** with cinnamoyl chloride, NEt_3, and DMAP yielded *epi*-**33**, too). This meant that under Mitsunobu conditions cinnamate *epi*-**33** formed after activation of the CO_2H group (of the carboxylic acid **31**), the overall process representing a kind of "Mitsunobu esterification". There seems to be scarce precedence for such configurationally retentive esterifications. The acetate **35** formed from the secondary alcohol **34** without the epimer, which would have emerged from a "Mitsunobu inversion" (Scheme 7).[25] Acetate **37** emerged from a "Mitsunobu esterification" of the secondary alcohol **36** with a 70:30 preference over the Mitsunobu inversion product *epi*-**37**.[26,27]

Scheme 7. Ester Formations under Mitsunobu Conditions with Retention of the Configuration of the C–O Bond: Precedents for the "Mitsunobu Esterification" **31** → *epi*-**33** (Scheme 6)



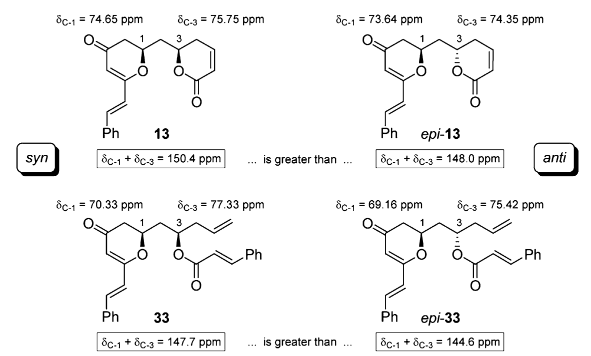
DEAD = diethyl azodicarboxylate; Ac = acetate

The terminating step of our approach to (+)-obolactone (**13**) was a ring-closing metathesis[28] of the homoallylic cinnamate **33** (Scheme 6, bottom).[29] Employing 5 mol % of the Grubbs II catalyst **13** resulted in 71% yield. Under the same conditions the epimeric cinnamate *epi*-**33** ring-closed to give 64% of the hitherto unknown (+)-*epi*-obolactone (*epi*-**13**). Starting from 1,5-dichloropentane-2,4-dione (**16**) our routes totaled 10 steps. The overall yields were 9% obolactone[30] (lit.[3] 15%, lit.[4] 2%, lit.[5] 9%) and 9% *epi*-obolactone.

The *syn*,*anti*-pairs **13**/*epi*-**13** and **33**/*epi*-**33** reveal a ^{13}C NMR difference shared by a variety of *O*,*O*-diprotected 1,3-diols $RCH_2C^1H(OR^1)C^2H_2C^3H(OR^3)CH_2R'$: The sum of the ^{13}C NMR shifts of nuclei C-1 and C-3 is higher in the *syn*- than in the *anti*-isomer (Scheme 8). In 1,3-diols and *O*-monoprotected 1,3-diols the same ^{13}C NMR criterion allows to distinguish *syn*- and *anti*-configurations safely.[31] Hydrogen bonding between the 1-O*H* and the 3-O*R* or 3-O*H* group was considered a prerequisite for this NMR effect.[31] This appeared plausible because it implies a clear conformational bias.[31] While the protected 1,3-diols of Scheme 8 lack hydrogen bonds the gradient $(\delta_{C\text{-}1} + \delta_{C\text{-}3})_{syn} > (\delta_{C\text{-}1} + \delta_{C\text{-}3})_{anti}$ persists, possibly because 1,3-spaced OR substituents favor different backbone conformers.[32]

Mono-Wacker oxidations of 1,ω-dienes have been rarely used synthetically. The success of our application should encourage other workers to consider it a worthwhile option.[33]

Scheme 8. Tentative Criterion for Differentiating *syn*- and *anti*-Configured *O*,*O*-Diprotected 1,3-Diols



More examples including derivatives of 1,3,5-triols: Table in Supporting Information.

Acknowledgment. We thank Dr. M. Keller (Institut für Organische Chemie, Universität Freiburg) for NMR spectra and the IRTG 1038 (DFG) for financial support.

Supporting Information Available. Experimental procedures, characterization data, copies of NMR spectra, Table Supplement to Scheme 8, and complete citation for ref 33. This material is available free of charge via the Internet at http://pubs.acs.org.

(29) Ring-closing metatheses of cinnamates yielding dihydro-α-pyranones: (a) Chandra, J. S.; Reddy, M. V. R.; Ramachandran, P. V. *J. Org. Chem.* **2002**, *67*, 7547–7550. (b) García-Fortanet, J.; Murga, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2003**, *5*, 1447–1449. (c) Murga, J.; García-Fortanet, J.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2004**, *69*, 7277–7283. (d) Díaz-Oltra, S.; Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2004**, *60*, 2979–2985. (e) Kiran, I. N. C.; Reddy, R. S.; Suryavanshi, G.; Sudalai, A. *Tetrahedron. Lett.* **2011**, *52*, 438–440.

(30) The specific rotation of our obolactone was $[\alpha]^{20}_D = +262$ (c = 0.15, $CHCl_3$). This equals the average value of the natural product $[[\alpha]^{20}_D = +286$ (c = 1.12, $CHCl_3$)][1] and the earlier synthetic specimens: $[\alpha]^{25}_D = +243$ (c = 1.35, $CHCl_3$),[3] $[\alpha]^{25}_D = +252$ (c = 1.20, $CHCl_3$),[4] and $[\alpha]^{25}_D = +260$ (c = 0.16, $CHCl_3$).[5] Our obolactone exhibited mp 115–117 °C, which matches the previously reported values of 116 °C[1] and 116–118 °C.[3,5]

(31) Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3980–3992.

(32) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054–2070. Hoffmann, R. W. *Angew. Chem.* **2000**, *112*, 2134–2150.

(33) Selected examples of Wacker-type reactions in natural product synthesis: (a) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200–14201. (b) Liao, X.; Zhou, H.; Wearing, X. Z.; Ma, J.; Cook, J. M. *Org. Lett.* **2005**, *7*, 3501–3504. (c) Paterson, I.; Razzak, M.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 3295–3298. (d) Fleck, M.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 6189–6191. Fleck, M.; Bach, T. *Angew. Chem.* **2008**, *120*, 6284–6286. (e) Deng, J.; Zhu, B.; Lu, Z.; Yu, H.; Li, A. *J. Am. Chem. Soc.* **2012**, *134*, 920–923. For a more extensive list of related references, see the Supporting Information.

The authors declare no competing financial interest.