ORGANIC LETTERS

2002
Vol. 4, No. 20
3447−3449

# Stereoselective Synthesis of Microcarpalide

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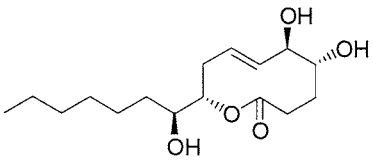
**Received July 17, 2002**

## ABSTRACT



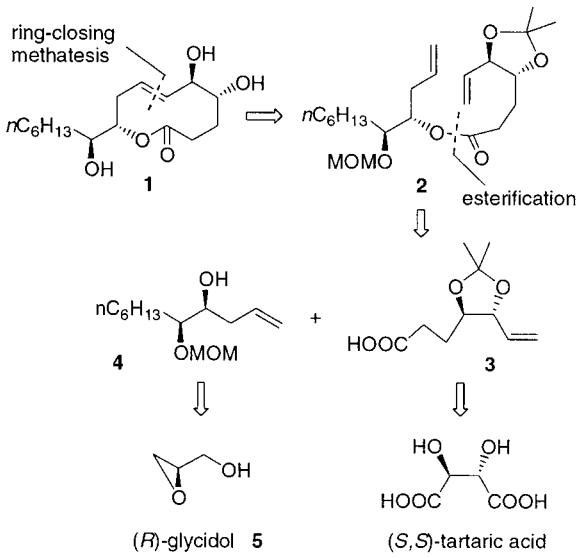

Microcarpalide

**The first total synthesis of the naturally occurring nonenolide, microcarpalide, is described. The key step in the synthesis was the ring-closing metathesis of a dienic ester prepared in turn by coupling an acid and an alcohol stereoselectively synthesized from (*S*,*S*)-tartaric acid and (*R*)-glycidol, respectively.**

From fermentation broths of an unidentified endophytic fungus growing on the bark of *Ficus microcarpa* L., T. Hemscheidt and co-workers were able to isolate a cytotoxic lactone, which they named microcarpalide. The compound showed strong antimicrofilament activity and was shown to have structure **1** by means of spectroscopic methods. Its absolute configuration was determined with the aid of the exciton chirality method.[1]

Within our recently initiated program on the synthesis of natural lactones using ring-closing metathesis (RCM) as one of the key steps,[2] we have devised a stereoselective syntheses for nonenolide **1**. The retrosynthetic analysis is depicted in Scheme 1. The macrocyclization step relies on a RCM of diolefinic ester **2**. Disconnection of the ester bond in **2** leads to chiral nonracemic fragments **3** and **4** (MOM = methoxymethyl),[3] derived in turn from (*S*,*S*)-tartaric acid and (*R*)-glycidol **5**, respectively.

**Scheme 1**




The known acid **3** was readily prepared from (*S*,*S*)-tartaric acid by means of a literature procedure.[4] Homoallylic alcohol **4** was prepared from **5** as described in Scheme 2. Silylation

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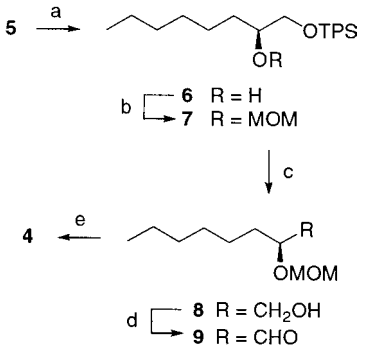
10.1021/ol0265463 CCC: $22.00 
**Published on Web 08/30/2002**

**Scheme 2**[a]

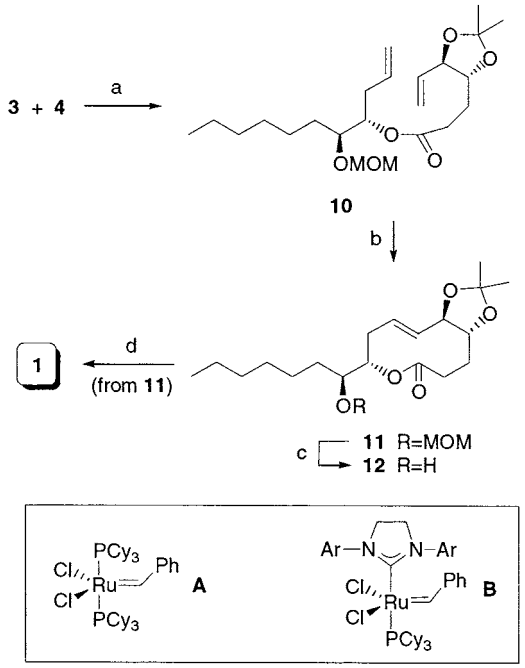



[a] Reagents and conditions: (a) (i) TPSCl, $Et_3N$, DMAP, $CH_2Cl_2$, rt, 18 h, 93%; (ii) $CH_3(CH_2)_4MgBr$, CuI, THF, −30 °C, 87%. (b) MOMCl, $Et_3N$, DMAP, $CH_2Cl_2$, rt, 18 h, 87%. (c) TBAF, THF, 5 h, rt, 93%. (d) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78 °C, 30 min, then *N*,*N*-diisopropyl ethylamine, 2 min at −78 °C, then rt. (e) $Bu_3SnCH_2CH{=}CH_2$, $MgBr_2{\cdot}Et_2O$, 3 Å MS, $CH_2Cl_2$, 3 h at −78 °C, then 1.5 h at −40 °C, 60% combined yield of the two last steps.

of the hydroxyl group of **5**[5] followed by epoxide opening with a *n*-pentyl cuprate reagent[6] afforded alcohol **6**, which was then protected as its MOM derivative **7**. Desilylation of the latter to **8** followed by Swern oxidation under mild conditions[7] afforded α-alkoxy aldehyde **9**[8] which, without purification, was immediately allowed to react with allyl tri-*n*-butylstannane in the presence of $MgBr_2{\cdot}Et_2O$ (chelation control conditions).[9] This provided **4** in good yield and with high stereoselectivity (dr was judged to be ≥98%, as the minor stereoisomer was not detected by means of high-field $^1H$ and $^{13}C$ NMR).

Carboxylic acid **3** was then coupled with alcohol **4** to yield diene ester **10** (Scheme 3). This reaction set the stage for the crucial RCM, which was successful with ruthenium catalyst **A**.[10] Thus, a 0.001 M solution of **10** and 20 mol % of **A** was heated at reflux for 24 h in dry, degassed $CH_2Cl_2$. This provided a 2:1 *E*/*Z* mixture of macrocyclic lactones from which the (*E*)-isomer **11** was isolated by means of column chromatography on silica gel. It is worth mentioning here that the use of the second-generation ruthenium catalyst **B**[11] gave rise to the almost exclusive formation of (*Z*)-**11**. Similar

**Scheme 3**[a]




[a] Reagents and conditions: (a) DCC, DMAP, $CH_2Cl_2$, rt, 18 h, 86%. (b) 20 mol % of catalyst **A**, $CH_2Cl_2$, reflux, 24 h (see text), 67%. (c) $SMe_2$, $BF_3{\cdot}Et_2O$, −10 °C, 30 min, 71%. (d) $(CH_2SH)_2$, $BF_3$, $CH_2Cl_2$, 0 °C, 1 h, 66%.

differences in behavior between these catalyst types have previously been observed by Fürstner and co-workers in their approach to other natural nonenolides.[12] One of the catalysts these authors used was structurally similar to **A** but had an indenylidene group instead of the benzylidene moiety. The other catalyst was close to **B** but with an additional C=C bond in the imidazole ring. They attributed the different stereochemical outcome to the higher activity of the imidazolylidene-substituted catalyst, which was able to isomerize the C=C bond of the RCM product. In consequence, the *E*/*Z* ratio was no longer kinetically controlled but rather the result of a chemical equilibrium. This caused a marked enhancement in the percentage of the (*Z*)-isomer, which in

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(5) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437−475.

(6) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135−631.

(7) Dondoni, A.; Perrone D. *Synthesis* **1997**, 527−529. Racemization of aldehyde **8** was minimized when *N*,*N*-diisopropyl ethylamine was used as the base (ee of **8** was judged to be ≥98% in an indirect way, because no minor stereoisomers were detected by high-field NMR analysis of crude ester **10**).

(8) Both racemic and enantiomerically pure (*R*)-**9** have been previously synthesized using a different methodology. See: (a) Banfi, L.; Bernardi, A.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1984**, *49*, 3784−3790. (b) Banfi, L.; Cabri, W.; Poli, G.; Potenza, D.; Scolastico, C. *J. Org. Chem.* **1987**, *52*, 5452−5457.

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(10) (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (b) Trnka, T.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

(11) For recent examples of uses of this catalyst type, see: (a) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, 2247−2250. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (c) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751−1753. (d) Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517−1519. (e) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847−1850. (f) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145−2147. (g) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153−3155. (h) Ackermann, L.; El Tom, D.; Fürstner, A. *Tetrahedron* **2000**, *56*, 2195−2202. (i) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204−2207. (j) Heck, M. P.; Baylon, C.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2001**, *3*, 1989−1991. (k) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045−2048.

(12) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061−7069. For creation of medium-sized rings via RCM and previous examples of reversibility during these processes, see pertinent citations in this paper. Catalyst A is also able to induce *E*-*Z* isomerizations: Kalesse, M.; Quitschalle, M.; Claus, M.; Gerlach, K.; Pahl, A.; Meyer, H. H. *Eur. J. Org. Chem.* **1999**, 2817−2823.

their molecules was shown to be the thermodynamically more stable one. In the case of lactone **11**, theoretical calculations have shown that the (*Z*)-isomer is more stable than the (*E*)-isomer by about 2 kcal/mol.[13] Consequently, the same explanation proposed by Fürstner et al. might be valid here.

Selective removal of the MOM group in **11** was feasible under mild conditions[14] and furnished acetonide **12**, the properties of which (NMR, MS) were identical to those reported.[1] Preparation of the target molecule **1** was finally achieved by one-pot removal of all protecting groups in compound **11**.[15] The physical and spectral properties of synthetic **1** turned out to be identical to those reported for the natural compound. As reported by Hemscheidt and coworkers for the natural product,[1] the NMR spectra of synthetic **1** at room temperature revealed the presence of two slowly interconverting conformers in an approximate 3−3.5:1 ratio.

(13) Theoretical calculations were first performed at the semiempirical level (AM1) and gave a difference in energy contents of 2 kcal/mol between both stereoisomers. When the calculations were made with ab initio methods (HF/3-21G), the difference turned out to be 1.9 kcal/mol.

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In summary, a convergent, stereoselective synthesis of the pharmacologically active lactone **1** has been achieved with two commercially available, chiral reagents (*R*)-glycidol and (*S*,*S*)-tartaric acid as the starting materials. Minor modifications of the synthetic route described above will lead to nonnatural diastereoisomers of the natural lactone, to be used for studies on relationships between structure and pharmacological activity. Such studies are underway and will be published soon.

**Acknowledgment.** Financial support has been granted by the Spanish Ministry of Education (DGICYT project BQU2002-00468) and by BANCAJA (Project P1B99-18). J.M. thanks the Spanish Ministry of Science and Technology for a Ramón y Cajal fellowship.

**Supporting Information Available:** $^{1}H$ and $^{13}C$ NMR spectra of compounds **10**−**12** and **1**, optical rotation values and tabulated IR data of **10**−**12** and **1**, and MS data of **10**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0265463