Total Synthesis

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Enantioselective Total Synthesis of Terreumols A and C from the Mushroom *Tricholoma terreum*

*Alex Frichert, Peter G. Jones, and Thomas Lindel**

Dedicated to Professor Henning Hopf on the occasion of his 75th birthday

Abstract: *The cytotoxic meroterpenoids terreumol A and C from the grey knight mushroom Tricholoma terreum were synthesized for the first time. The key step of the enantioselective total synthesis of terreumol C is a ring-closing metathesis to form a trisubstituted Z double bond embedded in the 10-membered ring of the [8.4.0] bicycle. Interestingly, the presence of a free hydroxy group in the metathesis precursor prevents cyclization and favors cross metathesis. (−)-Terreumol C was converted into (−)-terreumol A by diastereoselective epoxidation. Starting from 2-bromo-3,5-dimethoxybenzaldehyde, 14 steps with an overall yield of 23% are needed for the synthesis of (−)-terreumol A. X-ray analysis of the benzoquinone analogue of terreumol A provides independent proof of the absolute configuration.*

The terreumols from the mushroom *Tricholoma terreum* are unique meroterpenoids that were described by Liu and coworkers in 2013.[1] Characteristically, the terreumols contain an [8.4.0] bicycle with a methoxy-substituted hydroquinone moiety and a terpenoid ten-membered ring. (−)-Terreumol A (**1**, Figure 1) is a bisepoxide, whereas (−)-terreumol C (**2**) exhibits only one epoxide partial structure.

To date, little is known about the biological activity of terreumols, with the exception of cytotoxicity, for which half maximal inhibitory concentrations (IC_{50}) values have been reported in the single-digit and low double-digit micromolar range, which is comparable to cisplatin. There is also interest in mushrooms of the genus *Tricholoma* because cases of poisoning by rhabdomyolysis have been reported.[2] Further research on the biological activities or derivatization will only be possible if the terreumols can be accessed by total synthesis.

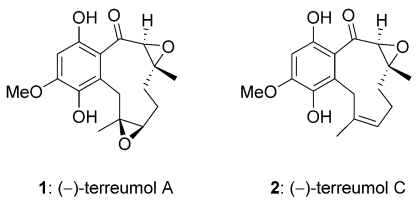
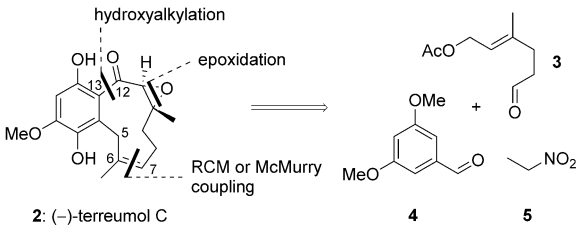


Figure 1. Terreumols A–D from the mushroom *Tricholoma terreum*.

A few other natural products share the partially aromatic [8.4.0] bicycle with the terreumols.[3] Among them, the clavilactones from the basidiomycete *Clitocybe claviceps* have received the greatest attention, and several total syntheses have been developed.[4–7] As part of our work on diterpenoids, we have shown that [8.4.0] systems with a benzene partial structure are accessible through intramolecular aldehyde/ketone McMurry coupling for closing of the ten-membered ring.[8] Therefore, we included McMurry coupling in our retrosynthesis, in addition to ring-closing metathesis (RCM; Scheme 1). It was unclear, however, whether the desired *trans* configuration of the epoxide moiety in (−)-terreumol C (**2**) would allow cyclization. Both routes would start from the same precursors: **3**, **4**, and **5**.



Scheme 1. Retrosynthetic analysis of (−)-terreumol C. Position numbering according to Ref. [1].

For the synthesis of the pentasubstituted benzene moiety, 2-bromo-3,5-dimethoxybenzaldehyde (**6**)[9] was converted into the nitrostyrene, followed by reduction to the imine/enamine (Fe, HOAc) and hydrolysis to phenylpropanone **7** (Scheme 2). After protection of the ketone as 1,3-dioxolane (**8**), the bromo substituent was replaced by a hydroxy function through Br/Li exchange, conversion into the dimethylboronate, and oxidative hydrolysis with H_2O_2/Na_2CO_3(aq.) to **9** (90%). Surprisingly, attempts at phenol bromination with either NBS or $PhMe_3NBr_3$ afforded the tetrasubstituted undesired benzofuran **10** in quantitative yield. Bromination of the aryl ring was still faster than electrophilic ring opening of the 1,3-dioxolane but did not occur exclusively. The

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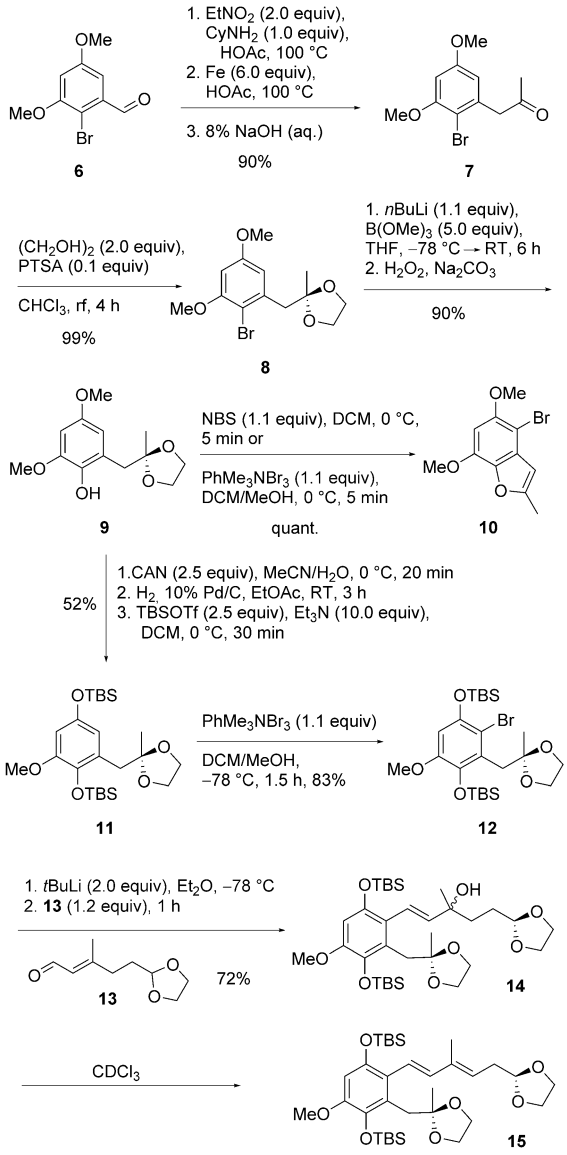
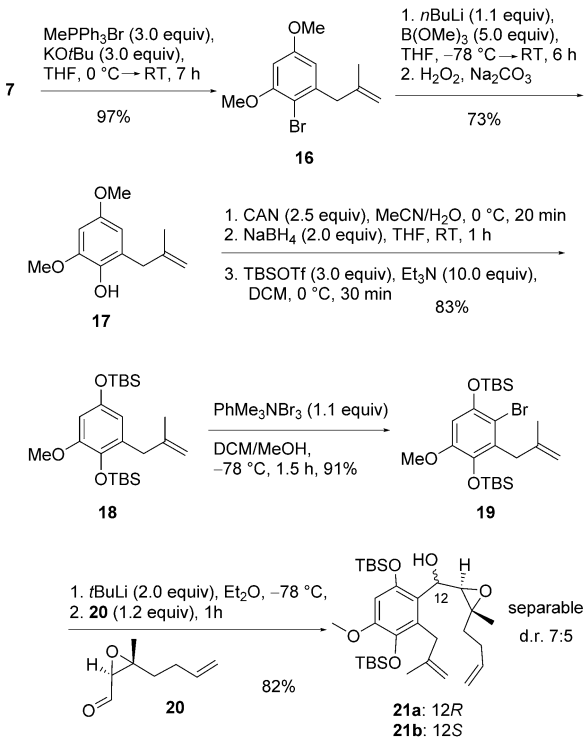


Scheme 2. Synthesis and hydroxyalkylation of sterically congested phenylbromide **12**. CAN = ceric ammonium nitrate, Cy = cyclohexyl, DCM = dichloromethane, NBS = *N*-bromosuccinimide, PTSA = toluene-*p*-sulfonic acid, rf = reflux, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

phenolic hydroxy group needed to be protected. Treatment of **9** with CAN led to regioselective demethylation an the *p* position and formation of the *p*-benzoquinone, which afforded bis(TBS) ether **11** after reduction and silylation (Scheme 2). Bromination in the *para* position to the remaining OMe group ($PhMe_3NBr_3$) afforded the pentasubstituted benzene derivative **12**.

An unexpected problem occurred in the hydroxyalkylation of **12** with α,β-unsaturated aldehyde **13**, which was prepared in 6 steps from geraniol.[10] After bromine/lithium exchange (*t*BuLi, Et_2O) and reaction with aldehyde **13**, we isolated the inverted tertiary allylic alcohol **14** (72% yield), which in $CDCl_3$ underwent elimination to diene **15** and other products. Conversion to the required epoxy ketone moiety of

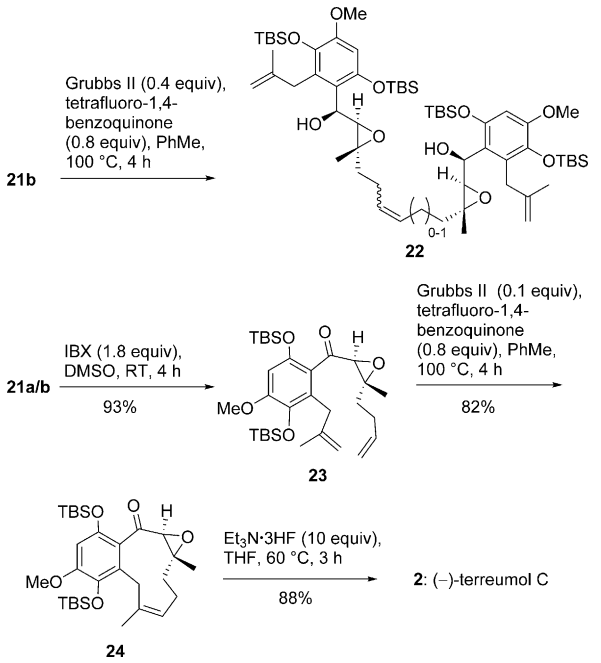


Scheme 3. Synthesis of metathesis precursors **21a**,**b**.

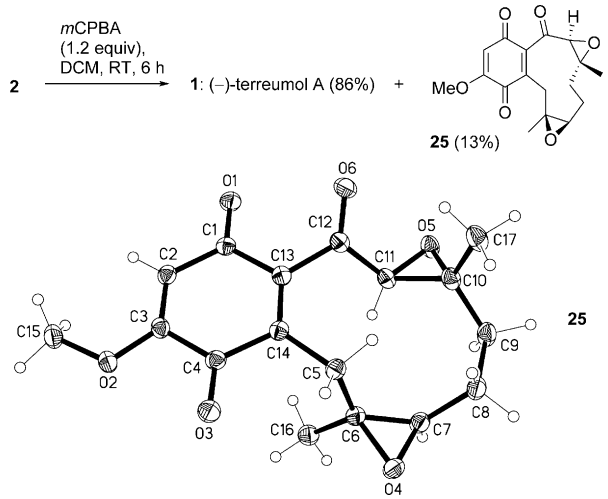
the terreumols seemed impossible. Therefore, we turned to RCM.

For synthesis of the RCM precursors, ketone **7** was methylenated (**16**, 97%, Scheme 3), followed by Br/OH exchange, oxidative O-demethylation, reduction to the hydroquinone, and double silylation to afford compound **18** (59% over five steps). Bromination ($PhMe_3NBr_3$, CH_2Cl_2/MeOH, −78 °C) afforded aryl bromide **19**, which was hydroxyalkylated after bromine/lithium exchange (*t*BuLi, 82%) with epoxyaldehyde **20**,[11] which was synthesized through Katsuki–Sharpless epoxidation. We obtained diastereomers **21a**,**b**, which could be separated by column chromatography, in an almost equimolar ratio (7:5).[12] However, when reacting either **21a** or **21b** in the presence of substoichiometric amounts of Grubbs II catalyst (40 mol%) and tetrafluorobenzoquinone (80 mol%) for oxidation of the ruthenium hydride species,[13] we did not observe cyclization to the ten-membered ring (Scheme 4). Instead, reaction of **21b** provided **22** as a mixture of *E*/*Z* isomers by cross metathesis. A product shortened by one methylene group was also formed, despite the addition of tetrafluorobenzoquinone. Similar observations have been made in the course of RCM to cyclooctenes with trisubstituted double bonds,[14] and also in the absence of quinone additives.[15,16]

The picture changed after oxidation of **21a**,**b** to epoxyketone **23**. In this case, 82% yield of the [8.4.0] bicycle **24** was obtained, together with minor amounts of open-chain material, which could be separated by chromatography (Scheme 4). The natural product (−)-terreumol C (**2**) was obtained as yellow crystals after double desilylation of **24** (88%, NEt_3·3HF, Scheme 4). The NMR data of the synthe-



Scheme 4. Ring-closing metathesis to give (−)-terreumol C (**2**). IBX = *o*-iodoxybenzoic acid.



Scheme 5. Oxidation of (−)-terreumol C (**2**) to (−)-terreumol A (**1**) and *p*-benzoquinone **25**, for which an X-ray structure was obtained. *m*CPBA = *meta*-chloroperbenzoic acid.

sized and isolated natural product in [D_6]acetone agreed completely. NOESY analysis allowed assignment of the diastereotopic hydrogen atoms and showed that the preferred conformation in [D_6]acetone is the same as in the crystal structure obtained by Liu et al. The specific optical rotation of the synthesized product **2** was about 10% smaller than reported for the isolated sample ($[\alpha]_D^{21} = -50.0°$ ($c = 0.17$, MeOH) compared to $[\alpha]_D^{20} = -55.5°$ ($c = 0.17$, MeOH)). This is probably a consequence of the *ee* that can be reached by the Katsuki–Sharpless epoxidation, which was employed for the synthesis of epoxyaldehyde **20**. By GC on a chiral column (Hydrodex-β-6TBDM, 25 m × 0.25 mm), we determined an *ee* of 89% for the alcohol precursor.

With (−)-terreumol C (**2**) in hand, we wondered whether (−)-terreumol A (**1**) would be accessible by diastereoselective epoxidation of the trisubstituted alkene moiety. There was a good chance since one face was expected to be buried in the inner sphere of the ten-membered ring. Indeed, treatment with *m*CPBA gave (−)-terreumol A (**1**) with perfect diastereoselectivity as a crystalline yellow solid (86%, $\lambda_{max} = 202$, 249, 291, 372 nm). All NMR data were in agreement with those reported. We measured a specific optical rotation of $[\alpha]_D^{22} = -221.7°$ ($c = 0.29$, MeOH) which compares well with the reported value ($[\alpha]_D^{20} = = -216.1°$ ($c = 0.29$, MeOH)). We also isolated an over-oxidized side product (**25**, 13%, Scheme 5), which turned out to be the *p*-benzoquinone. The absolute configuration of **25**, and thus of (−)-terreumol A (**1**), was confirmed by X-ray analysis (6*R*,7*S*,10*R*,11*S*).[17]

In summary, we have achieved the first total synthesis of the fungal natural products (−)-terreumol C (**2**) and (−)-terreumol A (**1**). Starting from 2-bromo-3,5-dimethoxybenzaldehyde, 13 steps with an overall yield of 26% were needed for the synthesis of (−)-terreumol C. (−)-Terreumol A was obtained in 14 steps and 23% overall yield. There are surprisingly few examples of the formation of medium-sized carbocycles by RCM. The formation of a trisubstituted double bond in a larger medium-sized carbocycle by RCM has been achieved by Yi and Hale in their formal total synthesis of the sesquiterpenoid (+)-eremantholide A,[18] by Harmata and co-workers in their total synthesis of the terpenoid buddledone A (11-membered ring),[19] and by Nicolaou and co-workers in their total synthesis of two floresolides.[20] In the latter case, competing cross metathesis had occurred. The influence of the distance of hydroxy groups and alkene moieties on the outcome of RCM has only been subject to preliminary investigation.[21] For allylic alcohols, the hydroxy group accelerates RCM, as first analyzed by Hoye and co-workers.[22] However, for homoallylic alcohols, retardation of ring closing in favor of cross metathesis was observed by Hoveyda and co-workers and has been connected to the formation of an intramolecular O–H···Cl-[Ru] bridge.[23]

Acknowledgements

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Keywords: medium-sized rings · meroterpenoids · natural products · ring-closing metathesis · total synthesis

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[1] X. Yin, T. Feng, Z.-H. Li, Z.-J. Dong, J. K. Liu, *J. Nat. Prod.* **2013**, *76*, 1365–1368.
[2] X. Yin, T. Feng, J.-H. Shang, Y.-L. Zhao, F. Wang, Z.-H. Li, Z.-J. Dong, X.-D. Luo, J.-K. Liu, *Chem. Eur. J.* **2014**, *20*, 7001–7006.

[3] a) F. Gómez, L. Quijano, J. S. Calderón, T. Ríos, *Phytochemistry* **1980**, *19*, 2202 – 2203; b) A. Takahashi, G. Kusano, T. Ohta, S. Nozoe, *Chem. Pharm. Bull.* **1993**, *41*, 2032 – 2033; c) A. Arnone, R. Cardillo, S. V. Meille, G. Nasini, M. Tolazzi, *J. Chem. Soc. Perkin Trans. 1* **1994**, 2165 – 2168; d) S. Dettrakul, S. Surerum, S. Rajviroongit, P. Kittakoop, *J. Nat. Prod.* **2009**, *72*, 861 – 865.
[4] I. Larrosa, M. I. Da Silva, P. M. Gómez, P. Hannen, E. Ko, S. R. Lenger, S. R. Linke, A. J. P. White, D. Wilton, A. G. M. Barrett, *J. Am. Chem. Soc.* **2006**, *128*, 14042 – 14043.
[5] K. Takao, R. Nanamiya, Y. Fukushima, A. Namba, K. Yoshida, K. Tadano, *Org. Lett.* **2013**, *15*, 5582 – 5585.
[6] L. Lv, B. Shen, Z. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 4164 – 4167; *Angew. Chem.* **2014**, *126*, 4248 – 4251.
[7] H. Suizu, D. Shigeoka, H. Aoyama, T. Yoshimitsu, *Org. Lett.* **2015**, *17*, 126 – 129.
[8] M. Al Batal, P. G. Jones, T. Lindel, *Eur. J. Org. Chem.* **2013**, 2533 – 2536.
[9] Y.-R. Liao, P.-C. Kuo, S. C. Huang, *Tetrahedron Lett.* **2013**, *53*, 6202 – 6204.
[10] Aldehyde **13** was obtained from the alcohol by oxidation with IBX in EtOAc (see the Supporting Information). D.-L. Liang, N. Gao, W. Liu, *Molecules* **2014**, *19*, 1238 – 1249.
[11] Epoxyaldehyde **20** was obtained in two steps from (*E*)-3-methylhepta-2,6-dien-1-ylacetate (see the Supporting Information). C. W. Plummer, A. Soheili, J. L. Leighton, *Org. Lett.* **2012**, *14*, 2462 – 2464.
[12] Compounds **21a** and **21b** exhibit differing coupling constants ($^3J_{12H\text{-}13H}$ 6.6 vs. 9.0 Hz). **21a** ($\delta_{C12} = 67.6$, $\delta_{12\text{-}H} = 4.69$, $\delta_{13\text{-}H} = 3.26$ ppm, $CDCl_3$) is probably the (1(2*R*,13*R*) and **21b** ($\delta_{C12} = 69.7$, $\delta_{12\text{-}H} = 4.43$, $\delta_{13\text{-}H} = 3.17$ ppm, $CDCl_3$) the (1(2*S*,13*R*) diastereomer.
[13] S. H. Hong, D. P. Sanders, C. W. Lee, R. H. Grubbs, *J. Am. Chem. Soc.* **2005**, *127*, 17160 – 17161.
[14] G. De Bo, I. E. Markó, *Eur. J. Org. Chem.* **2011**, 1859 – 1869.
[15] K. Tsuna, N. Noguchi, M. Nakada, *Chem. Eur. J.* **2013**, *19*, 5476 – 5486.
[16] a) M. Michalak, J. Wicha, *Synlett* **2005**, 2277 – 2280; b) M. Michalak, J. Wicha, *Org. Biomol. Chem.* **2011**, *9*, 3439 – 3446.
[17] CCDC 1437572 (**25**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[18] Y. Li, K. J. Hale, *Org. Lett.* **2007**, *9*, 1267 – 1270.
[19] Z. Cai, N. Yongpruksa, M. Harmata, *Org. Lett.* **2012**, *14*, 1661 – 1663.
[20] K. C. Nicolaou, H. Xu, *Chem. Commun.* **2006**, 600 – 602.
[21] a) E. M. Codesido, L. Castedo, J. R. Granja, *Org. Lett.* **2001**, *3*, 1483 – 1486; b) R. García-Fandiño, M. J. Aldegunde, E. M. Codesido, L. Castedo, J. R. Granja, *J. Org. Chem.* **2005**, *70*, 8281 – 8290.
[22] T. R. Hoye, H. Zhao, *Org. Lett.* **1999**, *1*, 1123 – 1125.
[23] A. H. Hoveyda, P. J. Lombardi, R. V. O'Brien, A. R. Zhugralin, *J. Am. Chem. Soc.* **2009**, *131*, 8378 – 8379.

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