Natural Products

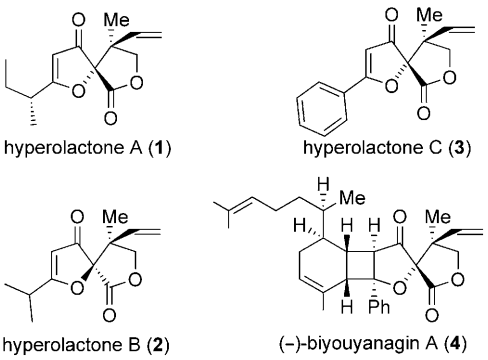
DOI: 10.1002/anie.200902908

Construction of Two Vicinal Quaternary Carbons by Asymmetric Allylic Alkylation: Total Synthesis of Hyperolactone C and (−)-Biyouyanagin A**

*Chao Du, Liqi Li, Ying Li, and Zhixiang Xie**

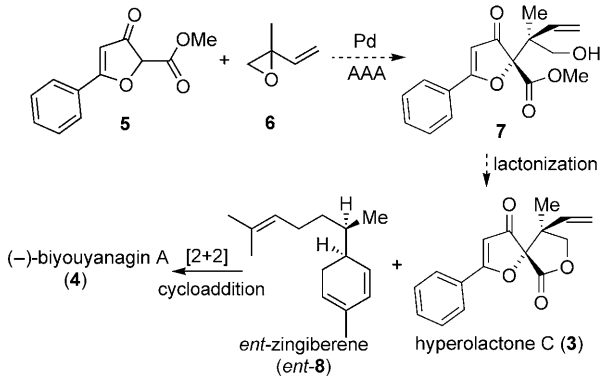
Dedicated to Professor Zhen Yang on the occasion of his 50th birthday

The motif of two vicinal quaternary carbon centers is found in a wide range of bioactive natural products such as hyperolactones A–C[1] and (−)-biyouyanagin A[2] (Scheme 1). The interesting biological activities and unique structures of these compounds have stimulated many total syntheses.[3] In general, the stereoselective construction of two vicinal quaternary carbon centers relys on substrate control. Only a few catalytic asymmetric C–C bond-forming reactions have been useful for constructing all-carbon quaternary stereocenters.[4] The catalytic asymmetric synthesis of two vicinal quaternary carbon centers with high diastereoselectivity and enantioselectivity remains a formidable challenge.



Scheme 1. Natural products with two vicinal quaternary carbon centers.

Palladium-catalyzed asymmetric allylic alkylation (Pd-AAA) reactions, which were pioneered by Trost et al., have proven to be a powerful method for the preparation of a wide variety of chiral building blocks with high diatereo- and enantioselectivity.[5] Trost et al. have also demonstrated the application of Pd-AAA reactions in the construction of single quaternary carbon centers.[6] However, to the best of our knowledge, there is no precedent for using Pd-AAA reactions to install two vicinal quaternary carbon centers. In our synthetic studies toward hyperolactone C (**3**) and (−)-biyouyanagin A (**4**), we have devised a novel synthetic strategy which features the use of Pd-AAA to construct the key vicinal quaternary carbon stereocenters. As shown in Scheme 2, we envisioned that if nucleophilic β-ketoester **5** and electrophilic allylic donor isoprene monoepoxide **6** could be coupled by a Pd-AAA reaction, then a short and efficient synthesis of hyperolactone C (**3**) could be realized after lactonization of the Pd-AAA product **7**. Subsequently, a photoinduced [2+2] cycloaddition reaction between hyperolactone C (**3**) and **8** would give (−)-biyouyanagin A (**4**). This strategy would not only provide a powerful method to construct two vicinal quaternary carbon centers in a highly stereoselective manner, but would also help gain entry to a range of hyperolactone C and biyouyanagin A analogues through diverted total synthesis.[7] Herein, we report our successful construction of two vicinal quaternary carbon centers by a Pd-AAA reaction. By using this strategy, concise and efficient total syntheses of hyperolactone C (**3**) and (−)-biyouyanagin A (**4**) have been achieved. The unnatural enantiomer, *ent*-hyperolactone C and (+)-biyouyanagin A, have also been prepared simply by switching the chiral ligand



Scheme 2. Proposed construction of two vicinal quaternary carbon centers and the synthetic plan for hyperolactone C and (−)-biyouyanagin A.

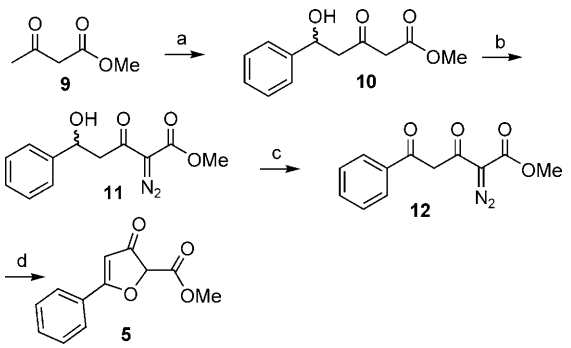
[*] C. Du, L. Li, Y. Li, Dr. Z. X. Xie
State Key Laboratory of Applied Organic Chemistry
College of Chemistry and Chemical Engineering
Lanzhou University, Lanzhou, 730000 (China)
E-mail: xiezx@lzu.edu.cn

[**] We are grateful for the financial support provided by the Basic Research Program (973 Program) of China (grant no. 2010CB833203) and the National Natural Science Foundation of China (grant nos. 20621091 and 20772050). We thank Mingji Dai (Columbia University) for helpful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200902908.

in the Pd-AAA reaction and changing the coupling partner in the photoinduced [2+2] cycloaddition reaction.

As shown in Scheme 3, the synthesis of the Pd-AAA precursor β-ketoester **5** commenced with benzaldehyde and methyl acetoacetate, which were converted into δ-hydroxy-β-oxo-pentanoate **10** by using the dianion method developed by Huchin and Weiler.[8] After treatment of **10** with TsN_3 in

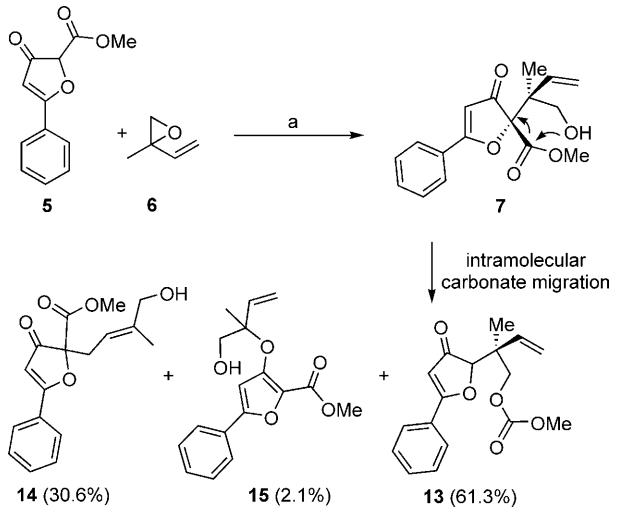


Scheme 3. Synthesis of β-ketoester **5**. Reagents and conditions: a) NaH, THF, 0 °C, 0.5 h; then *n*BuLi, THF, 0.5 h; benzaldehyde, THF, 2 h, 92%; b) TsN_3, Et_3N, MeCN, 2 h, 88%; c) DMP, CH_2Cl_2, 2 h, RT, 91%; d) $[Rh_2(OAc)_4]$, CH_2Cl_2, RT, 54%. DMP = Dess–Martin periodinane, THF = tetrahydrofuran, Ts = *p*-toluenesulfonyl.

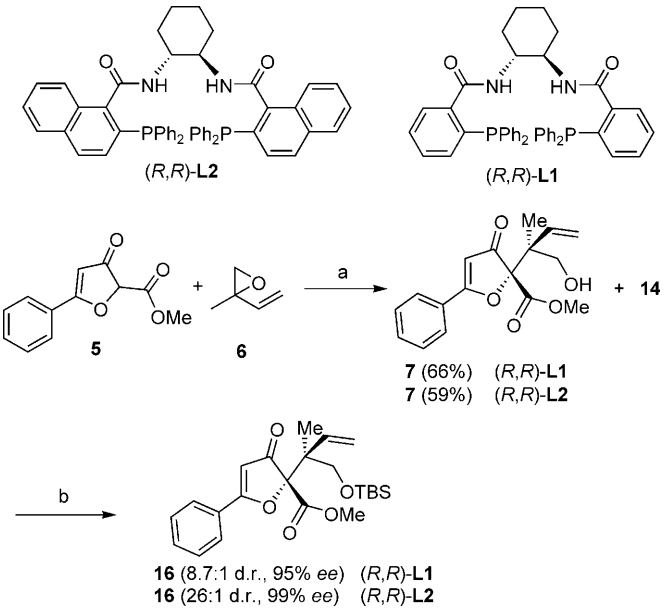
CH_3CN, the corresponding α-diazo-β-ketoester **11** was obtained in 88% yield.[9] Exposure of **11** to Dess–Martin periodinane in CH_2Cl_2 at room temperature led to the formation of the corresponding α-diazo-β-ketoesters **12**.[10] Then **12** was smoothly transformed into β-ketoester **5** in the presence of a catalytic amount of $[Rh_2(OAc)_4]$ in CH_2Cl_2 through a hydrogen migration process.[11]

With **5** in hand, the key Pd-AAA reaction was investigated. As shown in Scheme 4, β-ketoester **5** was treated with ligand (*R*,*R*)-**L1** (3 mol%) and $[Pd_2(dba)_3]\cdot CHCl_3$ (1 mol%) in the presence of isoprene monoepoxide **6**.[12] Upon quenching the reaction after 30 minutes at room temperature, none of the desired product **7** was isolated. After careful analysis of the ^1H and ^{13}C NMR spectra of all the compounds that were isolated, we found that the major product was **13** (61.3% yield) as well as **14** (30.6% yield) and **15** (2.1% yield). The formation of **13** suggested that the expected Pd-AAA reaction for the construction of the two vicinal quaternary carbon centers did take place, but that the branched product **7** underwent further intramolecular carbonate migration (see **7**→**13**) via a five-membered-ring intermediate to form **13** as a result of the prolonged reaction time.

The above hypothesis turned out to be correct: when the reaction was quenched within ten minutes, the desired branched product **7** and its linear isomer **14** were obtained in 66% and 31% yield, respectively (Scheme 5). Product **7** was unstable at room temperature and it slowly underwent



Scheme 4. Attempted Pd-AAA of ketone **5**. Reagents and conditions: a) (*R*,*R*)-**L1** (3 mol%; see Scheme 5 for structure), $[Pd_2(dba)_3]\cdot CHCl_3$ (1 mol%), CH_2Cl_2, RT, 30 min. dba = *trans*,*trans*-dibenzylideneacetone.

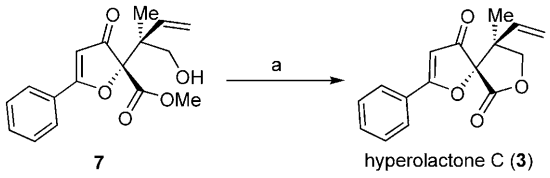


Scheme 5. Construction of two vicinal quaternary carbon centers by Pd-AAA. Reagents and conditions: a) (*R*,*R*)-**L1** or (*R*,*R*)-**L2** (3 mol%), $[Pd_2(dba)_3]\cdot CHCl_3$ (1 mol%), CH_2Cl_2, RT, 10 min; b) TBSCl, imid, DMF, RT, 75%. DMF = *N*,*N*-dimethylformamide, imid = imidazole, TBS = *tert*-butyldimethylsilyl.

lactonization to form hyperolactone C (**3**). After separation of the isomers, the primary alcohol of **7** was protected as its TBS ether **16**. It was found that the Pd-AAA reaction took place with high diastereoselectivity (8.7:1) and excellent enantioselectivity (95% *ee*), even though a low branched to linear regioisomeric ratio was obtained (**7**/**14** = 2.1:1). To improve the selectivity of the reaction, ligand (*R*,*R*)-**L2** was used. This time the desired product **7** was obtained with higher diastereoselectivity (26:1) and better enantioselectivity (99% *ee*), but in slightly lower yields for both **7** (59%) and **14** (26%). When ligand (*R*,*R*)-**L2** was switched to (*S*,*S*)-**L2**, *ent*-**7** could be synthesized (Table 1, entry 2).

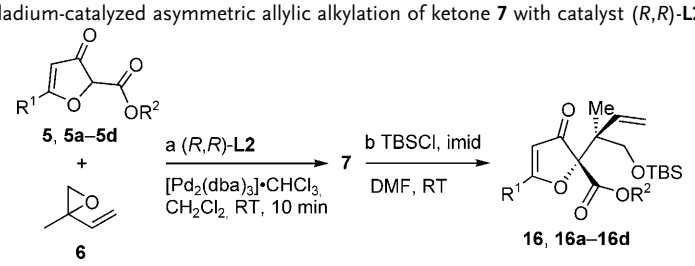
With these optimized reaction conditions, we sought to probe the scope of the Pd-AAA reaction with respect to the

nature of the β-ketoester component. Therefore, β-ketoesters **5a–5d** were prepared by a similar protocol to that described in Scheme 3. As summarized in Table 1, **5a–5d** reacted smoothly with isoprene monoepoxide **6** under the reaction condition developed with (*R*,*R*)-**L2** as the chiral ligand. Substrates with various substitution patterns gave the expected products in moderate yield, with high diastereoselectivity, and excellent enantioselectivity (99% *ee*). Both electron-rich (entry 3) and electron-poor (entry 4) functionalities on the aromatic ring could be accommodated. Isopropyl and benzyloxyethyl substitutents (entries 5 and 6) also gave similar results.



Scheme 6. Synthesis of hyperolactone C. Reagents and conditions: a) PTSA (20 mol%), CH_2Cl_2, RT, 1 h, 85%. PTSA = toluene-*p*-sulfonic acid.

Table 1: Palladium-catalyzed asymmetric allylic alkylation of ketone **7** with catalyst (*R*,*R*)-**L2**.



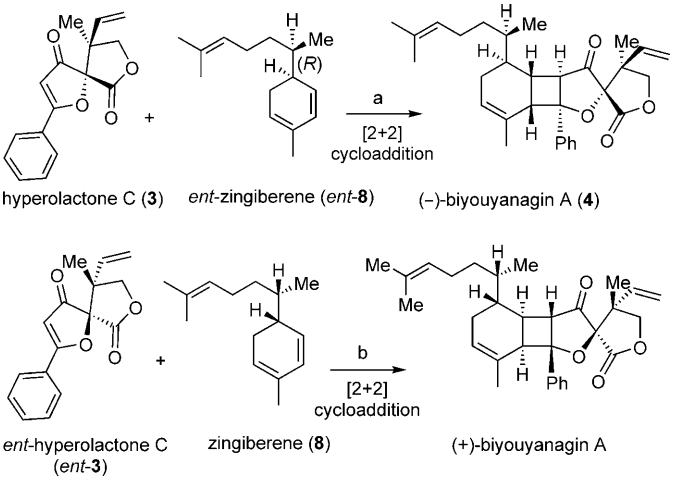
Entry	Substrate	d.r. (**7**/**14**)[a]	Product[b]	Yield [%][c]	*ee* [%][a]
1	**5** (R^1 = Ph, R^2 = Me)	26:1 (2.1:1)	**16**	59	99
2[d]	**5**	23:1 (*ent*-**7**/**14**=2.3:1)	*ent*-**16**	54	99
3	**5a** (R^1 = *p*-OMeC$_6$H$_4$, R^2 = Et)	32:1 (1.8:1)	**16a**	57	99
4	**5b** (R^1 = *p*-ClC$_6$H$_4$, R^2 = Et)	53:1 (1.6:1)	**16b**	68	99
5	**5c** (R^1 = isopropyl, R^2 = Me)	8.3:1 (2.8:1)	**16c**	55	99
6	**5d** (R^1 = $(CH_2)_2$OBn, R^2 = Me	56:1 (2.2:1)	**16d**	48	99

[a] **7**/**14** = regioisomeric ratio of branched to linear compounds. [b] Determined from analysis of the TBS ether **16** by HPLC on a chiral stationary phase. [c] Yield of isolated product **7** after column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 2:1). [d] (*S*,*S*)-**L2** was used. Bn = benzyl.

Having developed an efficient Pd-AAA protocol to construct the two vicinal quaternary carbon centers in hyperolactone C (**3**) and (-)-biyouyanagin A (**4**), we then proceeded to finish the total synthesis of hyperolactone C. As we mentioned before, intermediate **7** slowly underwent lactonization to generate hyperolactone C (**3**). This process was significantly accelerated by treatment with a catalytic amount of PTSA in CH_2Cl_2 at room temperature, and hyperolactone C (**3**) was generated with d.r. 26:1 in 85% yield after 1 hour (Scheme 6). Kraus and Wei[3d] reported that the diastereomer of **7**, which was isolated as the by-product in their elegant synthesis of racemic hyperolactone C, could not be converted into a lactone using heat, acid (PTSA), or base (*t*BuOK, NaH, or KH) catalysis. After careful analysis and comparison of the NMR data for both the by-product reported by Kraus and Wei and **13** obtained by us, we discovered that the so-called diastereomer of **7** was actually **13** (see the Supporting Information). The spectroscopic data of our synthetic hyperolactone C (**3**; ^{1}H, ^{13}C NMR, IR, and HRMS) are consistent with those of the natural product.[1] *Ent*-hyperolactone C was also prepared by us using the same method.

To synthesize (−)-biyouyanagin A (**4**), *ent*-zingiberene (*ent*-**8**)[13] was prepared according to the procedure reported by Nicolaou et al.[3f,g] The preparation of **4** was achieved by employing the reported biomimetic photoinduced [2+2] cycloaddition (Scheme 7).[3f,g,14] All the spectroscopic data of synthetic (−)-biyouyanagin A (**4**; ^{1}H, ^{13}C NMR, IR, and HRMS) are consistent with those of the natural product.[2] (+)-Biyouyanagin A, which is the unnatural enantiomer of (−)-biyouyanagin A (**4**), could also been synthesized through the [2+2] cycloaddition of *ent*-hyperolactone C (*ent*-**3**) and zingiberene (**8**; Scheme 7). Compound **8** was isolated from the powder *Zingiber officinale Roscoe*.[15] Notably, irradiation of a mixture of zingiberene (**8**) and hyperolactone C (**3**) under the same reaction condition led to a complex mixture.

In summary, we have developed a successful strategy for the construction of two vicinal quaternary carbon centers with



Scheme 7. Total synthesis of natural (−)-biyouyanagin A (**4**) and its enantiomer (+)-biyouyanagin A. Reagents and conditions: a) *hν*, **3**, (1.0 equiv), *ent*-**8** (4.0 equiv), 2′-acetonaphthone (1.0 equiv), CH_2Cl_2, 5 °C, 8 h, 39%, b) *hν*, *ent*-**3**, (1.0 equiv), *ent*-**8** (6.0 equiv), 2′-acetonaphthone (1.0 equiv), CH_2Cl_2, 5 °C, 8 h, 43%.

high diatereoselectivity (up to 56:1) and excellent enantioselectivity (99% *ee*) by using a palladium-catalyzed asymmetric allylic alkylation reaction. This strategy has enabled the concise and efficient total syntheses of natural hyperolactone C and (−)-biyouyanagin A from benzaldehyde in only six and seven steps, respectively. The corresponding overall yields were 20% and 8%. The unnatural enantiomer *ent*-hyperolactone C and (+)-biyouyanagin A were also prepared by simply switching the chiral ligand in the Pd-AAA reaction and by changing the coupling partner in the final photoinduced [2+2] cycloaddition reaction.

Received: May 30, 2009
Revised: July 28, 2009
Published online: September 11, 2009

Keywords: asymmetric allylic alkylation · natural products · palladium · quaternary carbon centers

[1] a) Y. Aramaki, K. Chiba, M. Tada, *Phytochemistry* **1995**, *38*, 1419; b) X-ray structure: S. L. Crockett, W. Schuhly, F. Belaj, I. A. Khan, *Acta Crystallogr. Sect. E* **2004**, *60*, 2174.

[2] N. Tanaka, M. Okasaka, Y. Ishimaru, Y. Takaishi, M. Sato, M. Okamoto, T. Oshikawa, S. U. Ahmed, L. M. Consentino, K.-H. Lee, *Org. Lett.* **2005**, *7*, 2997.

[3] Hyperolactones: a) D. Ichinari, T. Ueki, K. Yoshihara, T. Kinoshita, *Chem. Commun.* **1997**, 1743; b) T. Ueki, D. Ichinari, K. Yoshihara, Y. Morimoto, T. Kinoshita, *Tetrahedron Lett.* **1998**, *39*, 667; c) T. Ueki, M. Doe, R. Tanaka, Y. Morimoto, K. Yoshihara, T. Kinoshita, *Heterocycl. Chem.* **2001**, *38*, 165; d) G. A. Kraus, J. Q. Wei, *Nat. Prod.* **2004**, *67*, 1039; e) D. M. Hodgson, D. Angrish, S. P. Erickson, J. Kloesges, C. H. Lee, *Org. Lett.* **2008**, *10*, 5553; biyouyanagin A: f) K. C. Nicolaou, D. Sarlah, D. M. Shaw, *Angew. Chem.* **2007**, *119*, 4792; *Angew. Chem. Int. Ed.* **2007**, *46*, 4708; g) K. C. Nicolaou, T. R. Wu, D. Sarlah, D. M. Shaw, E. Rowcliffe, D. R. Burton, *J. Am. Chem. Soc.* **2008**, *130*, 11114.

[4] a) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363; b) A. Steven, L. E. Overman, *Angew. Chem.* **2007**, *119*, 5584; *Angew. Chem. Int. Ed.* **2007**, *46*, 5488; c) B. M. Trost, C. H. Jiang, *Synthesis* **2006**, 369; d) D. J. van Steenis, T. Marcelli, M. Lutz, A. L. Spek, J. H. Maarseveen, H. Hiemstra, *Adv. Synth. Catal.* **2007**, *349*, 281.

[5] For reviews, see: a) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921; b) B. M. Trost, M. R. Machacek, A. Aponick, *Acc. Chem. Res.* **2006**, *39*, 747.

[6] a) B. M. Trost, C. H. Jiang, *J. Am. Chem. Soc.* **2001**, *123*, 12907; for constructing two chiral centers by AAA, see: b) B. M. Trost, K. L. Sacchi, G. M. Schroeder, N. Asakawa, *Org. Lett.* **2002**, *4*, 3427; c) B. M. Trost, K. Dogra, M. Franzini, *J. Am. Chem. Soc.* **2004**, *126*, 1944.

[7] a) J. T. Njardarson, C. Gaul, D. Shan, X. Y. Huang, S. J. Danishefsky, *J. Am. Chem. Soc.* **2004**, *126*, 1038; b) R. M. Wilson, S. J. Danishefsky, *J. Org. Chem.* **2006**, *71*, 8329.

[8] a) S. N. Huckin, L. Weiler, *J. Am. Chem. Soc.* **1974**, *96*, 1082; b) C. F. Xu, C. Y. Yuan, *Tetrahedron* **2005**, *61*, 2169.

[9] J. C. Heslin, C. J. Moody, *J. Chem. Soc. Perkin Trans. 1* **1988**, 1417.

[10] P. H. Li, M. M. Majireck, I. Korboukh, S. M. Weinreb, *Tetrahedron Lett.* **2008**, *49*, 3162.

[11] a) S. Bien, A. Gillon, *Tetrahedron Lett.* **1974**, *15*, 3073; b) A. Padwa, R. L. Chinn, S. F. Hornbuckle, Z. J. Zhang, *J. Org. Chem.* **1991**, *56*, 3271; c) D. J. Fairfax, D. J. Austin, S. L. Xu, A. Padwa, *J. Chem. Soc. Perkin Trans. 1* **1992**, 2837.

[12] B. M. Trost, C. H. Jiang, *Org. Lett.* **2003**, *5*, 1563.

[13] Isolation: a) A. Eschenmoser, H. Schinz, *Helv. Chim. Acta* **1950**, *33*, 171; b) J. A. Mills, *J. Chem. Soc.* **1952**, 4976; c) G. Uhde, G. Ohloff, *Helv. Chim. Acta* **1972**, *55*, 2621; synthesis: d) S. M. Mukherji, N. K. Bhattacharyya, *J. Am. Chem. Soc.* **1953**, *75*, 4698; e) D. Arigoni, O. Jeger, *Helv. Chim. Acta* **1954**, *37*, 881; f) G. D. Joshi, S. N. Kulkarni, *Indian J. Chem.* **1965**, *3*, 91; g) M. Ni, Z. Chen, B. Yan, *Huadong Huagong Xueyuan Xuebao* **1988**, *14*, 675; h) D. C. Breeden, R. M. Coates, *Tetrahedron* **1994**, *50*, 11123; i) J. B. Bhonsle, V. H. Deshpande, T. Ravindranathan, *Indian J. Chem. Sect. B* **1994**, *33*, 313.

[14] a) T. S. Cantrell, *J. Org. Chem.* **1974**, *39*, 3063; b) G. O. Schenck, J. Kuhls, C. H. Krauch, *Justus Liebigs Ann. Chem.* **1966**, *693*, 20.

[15] See the Supporting Information.

