Phosphomolybdic Acid Catalyzed Synthesis of 1,2,4,5-Tetraoxanes

Xing Yan, Jinglei Chen, Yun-Ting Zhu, Chunhua Qiao*

College of Pharmaceutical Science, Soochow University, 199 Ren Ai Road, Suzhou 215123, P. R. of China
Fax +86(512)65882092; E-mail: qiaochunhua@suda.edu.cn

Received 17 August 2011

Abstract: 1,1-Dihydroperoxides were converted into 1,2,4,5-tetraoxanes through condensation with the corresponding ketones in 36–91% yields using phosphomolybdic acid as the catalyst and anhydrous $MgSO_4$ as the water scavenger.

Key words: phosphomolybdic acid, catalysis, cyclic condensation, 1,2,4,5-tetraoxanes, peroxide

1,2,4,5-Tetraoxanes are a class of novel compounds containing two peroxide groups.[1] The peroxide group has been proven as the pharmacophore of the noted antimalarial drug artemisinin (**1**, Figure 1).[2] Artemisinin derivatives are the first-line treatments of *Plasmodium falciparum* malaria.[3] Since 1,2,4,5-tetraoxanes (e.g., **2**) were discovered as the promising alternatives to artemisinin derivatives in the 1990s,[4] numerous studies have been carried out to search for 1,2,4,5-tetraoxanes as new antimalarial lead compounds.[5] Compared with artemisinin and its derivatives, 1,2,4,5-tetraoxanes were much easier to be chemically synthesized. Moreover, some synthetic 1,2,4,5-tetraoxanes (e.g., **3**) showed enhanced in vitro and in vivo antimalarial activity.[5i,m] Recent researches have revealed that 1,2,4,5-tetraoxanes possess a variety of important biological activities (e.g., antitumor,[6] antituberculosis,[6b,d] fasciocidal).[7] The amazing structural motif and exciting properties of 1,2,4,5-tetraoxanes provide broad space to be fully investigated.

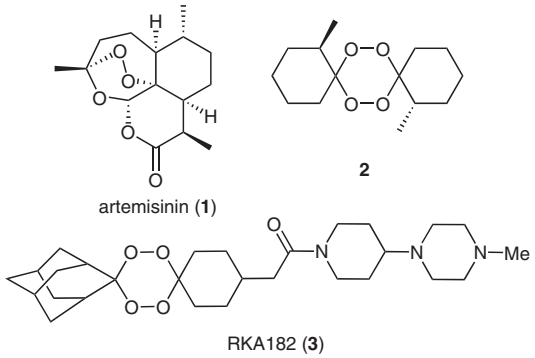


Figure 1 Peroxides with potent antimalaria activity

Symmetric 1,2,4,5-tetraoxanes can be obtained from condensation of carbonyl compounds with hydrogen peroxide catalyzed by a Brønsted acid,[4,5j] or with bis(trimethylsilyl) peroxide catalyzed by the Lewis acid TMSOTf.[5c,8] Ozonolysis of alkenes,[9] enol ethers,[10] or oximes[11] can also provide symmetric 1,2,4,5-tetraoxanes. Asymmetric 1,2,4,5-tetraoxanes are commonly prepared by condensations of carbonyl compounds (or ketal and acetal derivatives) with 1,1-dihydroperoxides [or bis-(trimethylsilyl) derivatives] catalyzed by H_2SO_4,[6d,e,12] MTO–HBF_4,[5l,13] Re_2O_7,[14] I_2–HBF_4,[15] $BF_3{\cdot}OEt_2$,[5k,16] or TMSOTf.[17] Among these catalysts, $BF_3{\cdot}OEt_2$, TMSOTf, and Re_2O_7 are highly moisture sensitive; MTO and Re_2O_7 are much expensive ($ 180/g and $ 150/g, respectively); I_2–HBF_4 was limited to aromatic aldehyde substrates.[5h,15] Furthermore, with the exception of Re_2O_7, condensation yields catalyzed by other acids were much lower, especially in H_2SO_4 (23–34%).[6d,e,12] Therefore, a more tolerant, inexpensive, and broadly applicable catalyst for the preparation of 1,2,4,5-tetraoxanes is needed.

Phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$) was reported as an efficient catalyst for the preparation of 1,1-dihydroperoxides[18] and the related β-hydroxyhydroperoxides.[19] In the course of investigation the PMA hydrate catalyzed preparation of 1,1-dihydroperoxides, we detected the formation of symmetric 1,2,4,5-tetraoxanes as minor byproducts. This accidental discovery inspired us to examine whether PMA could act as a catalyst in preparing symmetric and the more important asymmetric 1,2,4,5-tetraoxanes. PMA has numerous advantages including water compatibility, lower price ($ 3.8/g), and functional group tolerance of readily cleavable protecting groups (Bn, TBS, MOM, and allyl).[18,19] Herein, we report our investigation on PMA as an effective catalyst in preparing 1,2,4,5-tetraoxanes.

All 1,1-dihydroperoxides substrates (Figures 2, 5**a**–**h**) were prepared through the reactions of the corresponding ketones and aldehydes **4a**–**h** with ethereal hydrogen peroxide, employing PMA hydrate as the catalyst.[18]

Our initial investigation used ketone **4h** and 1,1-dihydroperoxide **5c** as substrates, applying commercial available PMA hydrate as a catalyst. The reaction afforded the desired product 1,2,4,5-tetraoxane **6** in a low, but promising yield (Table 1, entry 1). We speculated that the water of crystallization in PMA hydrate might adversely influence the condensation reaction by disturbing the substrates and PMA coordination. Therefore, commercial PMA was dehydrated in a microwave oven till a constant weight was observed. Employing the microwave-processed PMA; the reaction yield was improved from 27% to 39% (Table 1, entry 2). We subsequently pursued the optimization of the reaction conditions using dehydrated PMA.

SYNLETT 2011, No. 19, pp 2827–2830
Advanced online publication: 09.11.2011
DOI: 10.1055/s-0031-1289864; Art ID: W18311ST

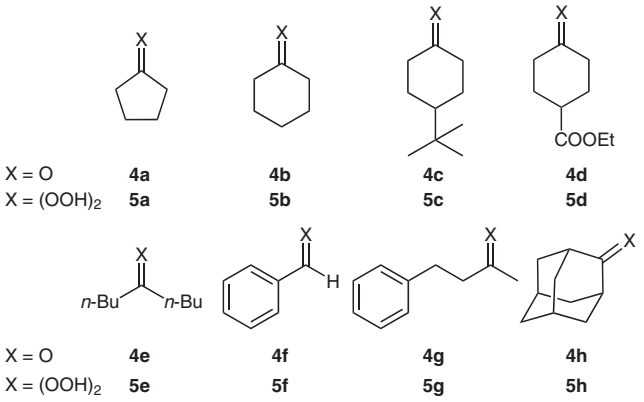
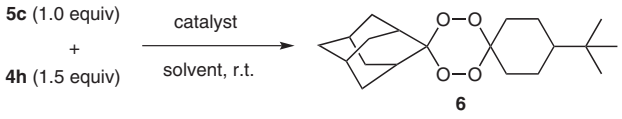


Figure 2 Ketones, aldehyde, and 1,1-dihydroperoxides used in this work

The catalyst loading was first optimized. As shown in Table 1, different amount of PMA (0.1–5 mol%, entries 3–7) afforded **6** in 38–50% yields. The optimal yield was achieved with a 1 mol% catalyst loading. Next, the solvent system was investigated (Table 1, entries 8–10). Both PMA (Table 1, entry 8) and PMA hydrate (Table 1, entry 9) exhibited limited solubility in diethyl ether resulting in much longer reaction times (20–22 h) and very low product yields (6–8%). In acetonitrile (Table 1, entry 10), the reaction was much faster, but the yield was substantially lower compared to CH_2Cl_2 (35% in MeCN vs. 50% in CH_2Cl_2). According to the above observations, 1 mol% PMA in CH_2Cl_2 was used as the optimal reaction conditions.

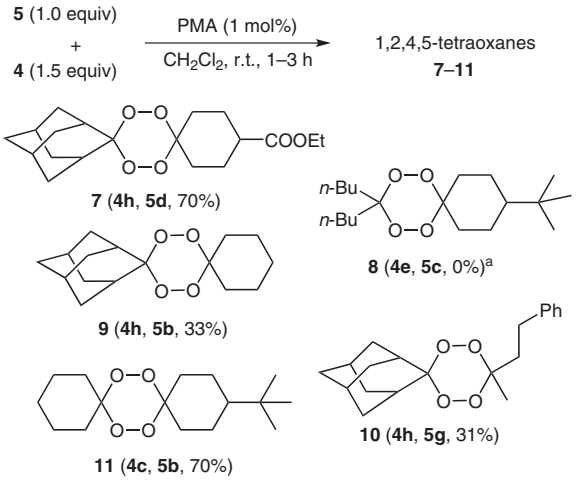
To explore the substrate tolerance to these optimized reaction conditions, a wide variety of 1,1-dihydroperoxides and carbonyl compounds was examined. As shown in Schemes 1, 1,2,4,5-tetraoxanes **7** and **11** were afforded in a moderate 70% yield, but yields of **9** and **10** were much lower. Especially in the case of compound **8**, it was very difficult to isolate the desired product as the reaction was very messy. Further examinations with aliphatic ketones as substrates should be explored to improve the product yield.

Table 1 Conditions and Yields in Model Reaction



Entry	Catalyst	Equiv (mol%)	Solvent	Time (h)	Yield (%)[a]
1	PMA hydrate	1	CH_2Cl_2	0.5	27
2	PMA	1	CH_2Cl_2	0.5	39
3	PMA	0.1	CH_2Cl_2	10	39
4	PMA	0.5	CH_2Cl_2	4	43
5	PMA	1	CH_2Cl_2	3	50
6	PMA	2	CH_2Cl_2	1	46
7	PMA	5	CH_2Cl_2	1	38
8	PMA	1	Et_2O	22	8
9	PMA hydrate	1	Et_2O	20	6
10	PMA	1	MeCN	0.25	35

[a] Isolated yield.



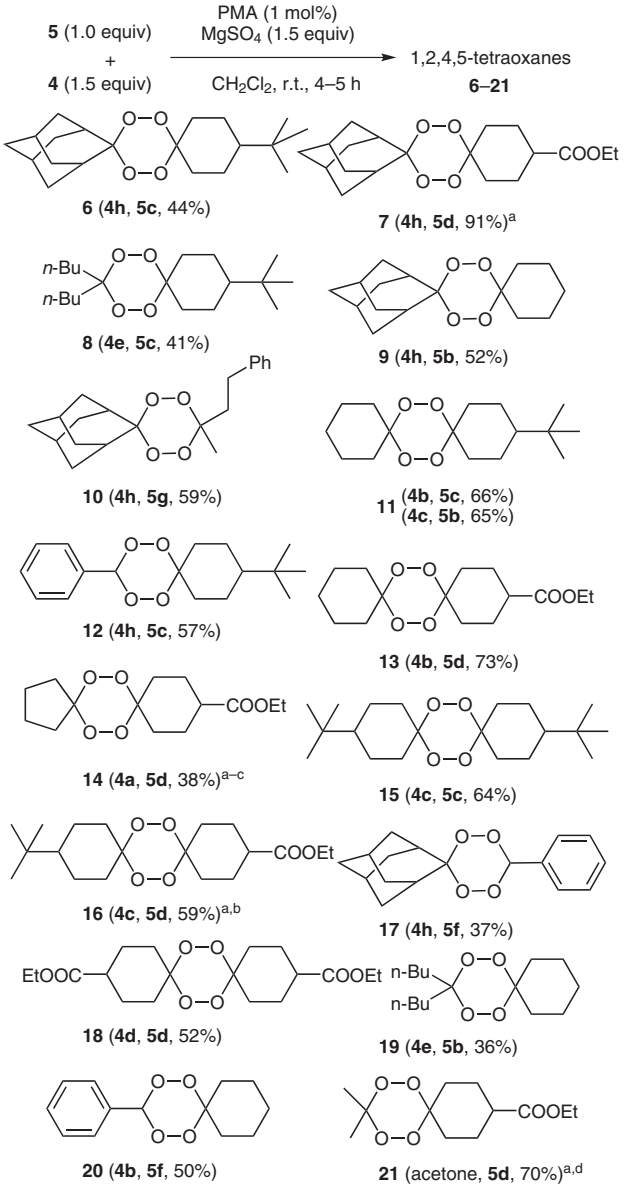
Scheme 1 Reaction details of 1,1-dihydroperoxides with carbonyl compounds without anhydrous $MgSO_4$ as desiccant. [a] The reaction mixture was too complex to purify.

In all cases, we observed that PMA was partially dissolved in CH_2Cl_2 in the beginning of the reaction. However, it slowly became stuck to the sides of the reaction vessel during the course of the reaction. We proposed that the water produced during the condensation reactions resulted in the conversion of PMA into its corresponding hydrate form, which might be even less soluble in CH_2Cl_2. It was reasonable to deduce that the reaction proceeded more slowly as a result of PMA precipitation. Moreover, the slow reaction resulted in the formation of undesired and difficult-to-separate byproducts. Following this logic, we hypothesized that addition of a desiccant to remove the produced water should enhance the reaction yield.

We first applied 4 Å molecular sieves as a desiccant, but hardly observed any yield improvement. Then anhydrous $MgSO_4$ was added due to its fast action, high capacity, and weak acidity.[20] Indeed, addition of 1.5 equivalents of anhydrous $MgSO_4$ to the reaction improved the reaction yields in most cases (Schemes 2, **7–10**), and reduced the formation of undesired byproducts. Highlighting the impact of $MgSO_4$ on the reaction, compound **8** could only be obtained with the addition of $MgSO_4$. Additionally, the yields of **7**, **9**, and **10** were improved by 20–30%.

Employing PMA-catalyzed condensation of 1,1-dihydroperoxides with ketones and aldehydes afforded asymmetric 1,2,4,5-tetraoxanes in moderate yields of 36–91% (Schemes 2, **6–21**), which were superior or comparable to the most efficient Re_2O_7, according to the yields reported[14] or checked by ourselves. For example, in the case that the substrate is possessing an ester group which

could be functionalized to carbonyl acid and alcohol (Scheme 2, entry **7**), the reaction yield was significantly higher in PMA (91%) vs. Re_2O_7 (72%). Another case with enhanced yield was with compound **10** (59% in PMA vs. 49%[14] in Re_2O_7). Other cases displayed a comparable yield including compounds **6** (44% vs. 48%); **8** (41% vs. 49%[14]); **9** (52% vs. 49%); **12** (57% vs. 66%[14]; yield in PMA vs. yield in Re_2O_7). In addition, the catalyst load dropped from 2–5 mol% in Re_2O_7 to 1 mol% in PMA. In addition, symmetric 1,2,4,5-tetraoxanes (**15** and **18**) could also be prepared in good yields (64% and 59%, respectively).



6 (**4h**, **5c**, 44%)
7 (**4h**, **5d**, 91%)[a]
8 (**4e**, **5c**, 41%)
9 (**4h**, **5b**, 52%)
10 (**4h**, **5g**, 59%)
11 (**4b**, **5c**, 66%) (**4c**, **5b**, 65%)
12 (**4h**, **5c**, 57%)
13 (**4b**, **5d**, 73%)
14 (**4a**, **5d**, 38%)[a–c]
15 (**4c**, **5c**, 64%)
16 (**4c**, **5d**, 59%)[a,b]
17 (**4h**, **5f**, 37%)
18 (**4d**, **5d**, 52%)
19 (**4e**, **5b**, 36%)
20 (**4b**, **5f**, 50%)
21 (acetone, **5d**, 70%)[a,d]

Scheme 2 Reaction details of 1,1-dihydroperoxides with carbonyl compounds employing anhydrous $MgSO_4$ as desiccant.[21] [a] New compounds. [b] Yield was determined on 0.5 g scale of 1,1-dihydroperoxides. [c] 36% on 5.5 g scale of **5d**. [d] Yield was determined in 7.4 g scale of **5d**.

In conclusion, PMA offers a highly efficient and practical method to prepare biologically active 1,2,4,5-tetraoxanes, employing the condensation reaction between 1,1-dihydroperoxides and carbonyl compounds. In comparison with other reported catalysts, such as Re_2O_7 and MTO, PMA is much less expensive; compared with the moisture-sensitive acids, such as TMSOTf and $BF_3{\cdot}OEt_2$. It is also substantially more stable in air and easy to handle. Moreover, the reported tolerance of various protecting groups[18,19] should promote its wider application.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was supported by Chinese National Science Foundation (81072514) to Professor Chunhua Qiao at Soochow University.

References and Notes

(1) (a) Dong, Y. X. *Mini-Rev. Med. Chem.* **2002**, *2*, 113. (b) Kumar, N.; Sharma, M.; Rawat, D. S. *Curr. Med. Chem.* **2011**, *18*, 3889.
(2) Brossi, A.; Venugopalan, B.; Dominguez Gerpe, L.; Yeh, H. J. C.; Flippen-Anderson, J. L.; Buchs, P.; Luo, X. D.; Milhous, W.; Peters, W. *J. Med. Chem.* **1988**, *31*, 645.
(3) *Guidelines for the Treatment of Malaria*, 2nd ed.; World Health Organization: Geneva, **2010**.
(4) Vennerstrom, J. L.; Fu, H. N.; Ellis, W. Y.; Ager, A. L. Jr.; Wood, J. K.; Andersen, S. L.; Gerena, L.; Milhous, W. K. *J. Med. Chem.* **1992**, *35*, 3023.
(5) (a) Todorovic, N. M.; Stefanovic, M.; Tinant, B.; Declercq, J. P.; Makler, M. T.; Solaja, B. A. *Steroids* **1996**, *61*, 688. (b) Dong, Y. X.; Matile, H.; Chollet, J.; Kaminsky, R.; Wood, J. K.; Vennerstrom, J. L. *J. Med. Chem.* **1999**, *42*, 1477. (c) Kim, H. S.; Shibata, Y.; Wataya, Y.; Tsuchiya, K.; Masuyama, A.; Nojima, M. *J. Med. Chem.* **1999**, *42*, 2604. (d) Vennerstrom, J. L.; Dong, Y. X.; Andersen, S. L.; Ager, A. L.; Fu, H. N.; Miller, R. E.; Wesche, D. L.; Kyle, D. E.; Gerena, L.; Walters, S. M.; Wood, J. K.; Edwards, G.; Holme, A. D.; McLean, W. G.; Milhous, W. K. *J. Med. Chem.* **2000**, *43*, 2753. (e) Opsenica, I.; Terzic, N.; Opsenica, D.; Milhous, W. K.; Solaja, B. *J. Serb. Chem. Soc.* **2004**, *69*, 919. (f) Atheaya, H.; Khan, S. I.; Mamgain, R.; Rawat, D. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1446. (g) Opsenica, D. M.; Terzic, N.; Smith, P. L.; Yang, Y.; Anova, L.; Smith, K. S.; Solaja, B. A. *Bioorg. Med. Chem.* **2008**, *16*, 7039. (h) Kumar, N.; Khan, S. I.; Beena; Rajalakshmi, G.; Kumaradhas, P.; Rawat, D. S. *Bioorg. Med. Chem.* **2009**, *17*, 5632. (i) O'Neill, P. M.; Amewu, R. K.; Nixon, G. L.; Bousejra ElGarah, F.; Mungthin, M.; Chadwick, J.; Shone, A. E.; Vivas, L.; Lander, H.; Barton, V.; Muangnoicharoen, S.; Bray, P. G.; Davies, J.; Park, B. K.; Wittlin, S.; Brun, R.; Preschel, M.; Zhang, K.; Ward, S. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 5693. (j) Dong, Y. X.; McCullough, K. J.; Wittlin, S.; Chollet, J.; Vennerstrom, J. L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6359. (k) Hamann, H. J.; Hecht, M.; Bunge, A.; Gogol, M.; Liebscher, J. *Tetrahedron Lett.* **2011**, *52*, 107. (l) Kumar, N.; Khan, S. I.; Atheaya, H.; Mamgain, R.; Rawat, D. S. *Eur. J. Med. Chem.* **2011**, 2816. (m) Marti, F.; Chadwick, J.; Amewu, R. K.; Burrell-Saward, H.; Srivastava, A.; Ward, S. A.; Sharma, R.;

Berry, N.; O'Neill, P. M. *Med. Chem. Commun.* **2011**, *2*, 661.
(6) (a) Opsenica, D.; Pocsfalvi, G.; Juranic, Z.; Tinant, B.; Declercq, J. P.; Kyle, D. E.; Milhous, W. K.; Solaja, B. A. *J. Med. Chem.* **2000**, *43*, 3274. (b) Solaja, B. A.; Terzic, N.; Pocsfalvi, G.; Gerena, L.; Tinant, B.; Opsenica, D.; Milhous, W. K. *J. Med. Chem.* **2002**, *45*, 3331. (c) Opsenica, R.; Angelovski, G.; Pocsfalvi, G.; Juranic, Z.; Zizak, Z.; Kyle, D.; Milhous, W. K.; Solaja, B. A. *Bioorg. Med. Chem.* **2003**, *11*, 2761. (d) Opsenica, D.; Kyle, D. E.; Milhous, W. K.; Solaja, B. A. *J. Serb. Chem. Soc.* **2003**, *68*, 291. (e) Terzic, N.; Opsenica, D.; Milic, D.; Tinant, B.; Smith, K. S.; Milhous, W. K.; Solaja, B. A. *J. Med. Chem.* **2007**, *50*, 5118. (f) Zizak, Z.; Juranic, Z.; Opsenica, D.; Solaja, B. A. *Invest. New Drugs* **2009**, *27*, 432.
(7) Kirchhofer, C.; Vargas, M.; Braissant, O.; Dong, Y. X.; Wang, X. F.; Vennerstrom, J. L.; Keiser, J. *Acta Trop.* **2011**, *118*, 56.
(8) Jefford, C. W.; Boukouvalas, A. J. J. *Synthesis* **1988**, 391.
(9) Murray, R. W.; Agarwal, S. K. *J. Org. Chem.* **1984**, *50*, 4698.
(10) Nakamura, N.; Nojima, M.; Kusabayashi, S. *J. Am. Chem. Soc.* **1987**, *109*, 4969.
(11) Dong, Y. X.; Vennerstrom, J. L. *J. Org. Chem.* **1998**, *63*, 8582.
(12) Opsenica, I.; Opsenica, D.; Smith, K. S.; Milhous, W. K.; Solaja, B. A. *J. Med. Chem.* **2008**, *51*, 2261.
(13) Ellis, G. L.; Amewu, R.; Sabbani, S.; Stocks, P. A.; Shone, A.; Stanford, D.; Gibbons, P.; Davies, J.; Vivas, L.; Charnaud, S.; Bongard, E.; Hall, C.; Rimmer, K.; Lozanom, S.; Jesus, M.; Gargallo, D.; Ward, S. A.; O'Neill, P. M. *J. Med. Chem.* **2008**, *51*, 2170.
(14) Ghorai, P.; Dussault, P. H. *Org. Lett.* **2009**, *11*, 213.
(15) Kumar, N.; Khan, S. I.; Sharma, M.; Atheaya, H.; Rawat, D. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1675.
(16) Terent'ev, A. O.; Kutkin, A. V.; Starikova, Z. A.; Antipin, M. Y.; Ogibin, Y. N.; Nikishina, G. I. *Synthesis* **2004**, 2356.
(17) Kim, H. S.; Tsuchiya, K.; Shibata, Y.; Wataya, Y.; Ushigoe, Y.; Masuyama, A.; Nojima, M.; McCullough, K. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1867.
(18) Li, Y.; Hao, H. D.; Zhang, Q.; Wu, Y. K. *Org. Lett.* **2009**, *11*, 1615.
(19) Li, Y.; Hao, H. D.; Wu, Y. K. *Org. Lett.* **2009**, *11*, 2691.
(20) Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry*, 2nd ed.; Stanley Thornes: Cheltenham, **1998**.
(21) **Representative Procedure for the Preparation of Adamantane-2-spiro-3′-1′,2′,4′,5′-tetraoxane-6′-spiro-4″-*tert*-butyl-1″-cyclohexane (6)**
A mixture of **4h** (88 mg, 0.59 mmol, 1.5 equiv), PMA (7 mg, 3.9 μmol, 1 mol%), and anhyd $MgSO_4$ (71 mg, 0.59 mmol, 1.5 equiv) in CH_2Cl_2 (3 mL) was stirred for 20 min at r.t. To this solution was added **5c** (80 mg, 0.39 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) in 15 min. The mixture was stirred at r.t. and monitored by TLC. When **5c** was consumed completely, H_2O (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried by anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatograph (PE–EtOAc = 400:1) to afford **6** (58 mg, yield 44%) as white solid; mp 136–138 °C (lit.[14] 134–136 °C). R_f = 0.79 (PE–EtOAc, 50:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.17 (s, 2 H), 1.97 (s, 4 H), 1.86 (s, 2 H), 1.82–1.51 (m, 9 H), 1.50–1.35 (m, 2 H), 1.35–1.15 (s, 3 H), 1.08 (m, 1 H), 0.86 (s, 9 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 110.4, 108.2, 47.6, 37.1, 34.5, 33.3, 32.6, 32.3, 29.8, 27.8, 27.2, 23.2.[14]