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A NEW METHOD OF DEUTERIUM INCORPORATION TO TMS-EPOXYALCOHOL USING SODIUM METHYLSULFINYLMETHYLIDE-d_5 (NaDMSO-d_5)[†]

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Abstract – A reaction of 1-TMS-1,2-epoxyoctan-3-ol with NaDMSO-d_5 (Na^+ $CD_3S(O)CD_2^-$), prepared in situ from DMSO-d_6 and NaH, afforded non-1-ene-1,1-d_2-3,4-diol. Both the anti and syn isomers showed similar reactivity and the stereochemistry was preserved. α-Ethoxyethyl ether of the epoxy alcohol was converted to the corresponding mono-ethoxyethyl ether of the 1-ene-3,4-diol. Hydroboration and hydrogenation of the corresponding TBS ethers afforded compounds with the "CH_2CD_2OH" and "CH_2CD_2H" groups, respectively.

Common deuterium sources for deuteration of organic compounds are deuterium oxide, deuterium gas, and metal deuterides such as $LiAlD_4$ and $NaBD_4$,[1] and several types of reactions have been used for each deuterium reagent.[2] Furthermore, new reactions using transition metal catalysts have been developed for deuteration.[3] Herein, we introduce a reaction using $(CD_3)_2SO$ (DMSO-d_6), which is available at a reasonable price.[4] Previously, a reaction of secondary TMS-epoxy (TMS: Me_3Si) alcohols with NaDMSO (Na^+ $MeS(O)CH_2^-$) was reported to afford 1-ene-3,4-diols via the epoxide ring opening followed by TMS migration to the alkoxy oxygen and subsequent elimination of sulfenic acid,[5] and thus, deuterium incorporation was expected with the anion derived from DMSO-d_6 and NaH. Herein, we report results of this study and further conversions, which would be useful for synthesis of deuterated fatty acid metabolites.[6] A DMSO-d_6 solution of NaDMSO-d_5 was prepared by mixing DMSO-d_6 (20 equiv) and NaH (7 equiv) as described (70 °C, 1 h),[7] and a THF solution of epoxy alcohols **1a/s** (a mixture of the anti (**a**) and syn (**s**) isomers) in a 43:57 ratio[8] was added to the anion at room temperature (rt). The reaction was carried out at rt for 3 h to afford diol **2a/s** in 65% yield (Table 1, entry 1). The anti/syn ratio was almost same as that of

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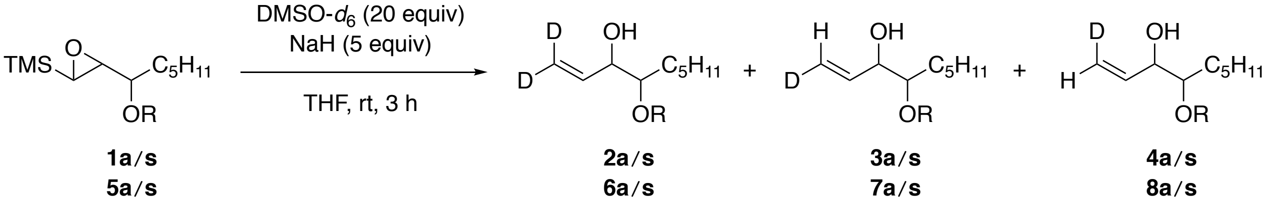
† This paper is dedicated to Professor Kiyoshi Tomioka on the occasion of his 70th birthday.

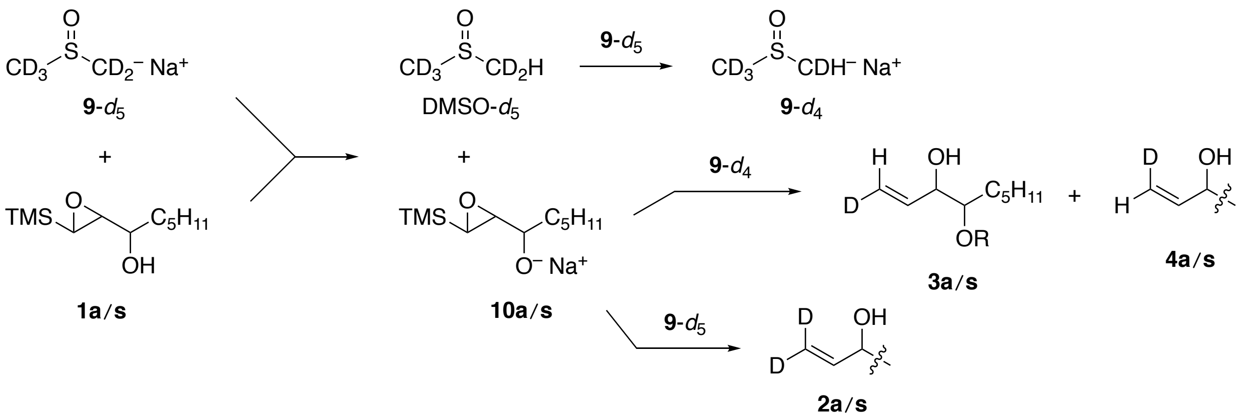
Table 1. Reaction of TMS-substituted epoxy alcohols with NaDMSO-d_5



entry	R	substrate	anti/syn	diol	yield	anti/syn	**2/3/4**[a]
1	H	**1a/s**	43:57[a]	**2a/s**	65%	43:57[a]	96:2:2
2	H	**1a**	100:0	**2a**	75%	100:0	96:2:2
3	H	**1s**	0:100	**2s**	65%	0:100	96:2:2
4	EE[b]	**5a/s**[c]	mixture[c]	**6a/s**	66%	mixture[c]	98:1:1[d]

[a] Determined by ^{1}H NMR spectroscopy. [b] α-Ethoxyethyl. [c] Derived from **1a/s** (ca. 1:1) and CH$_2$=CHOEt. [d] Ratio of **6/7/8**.

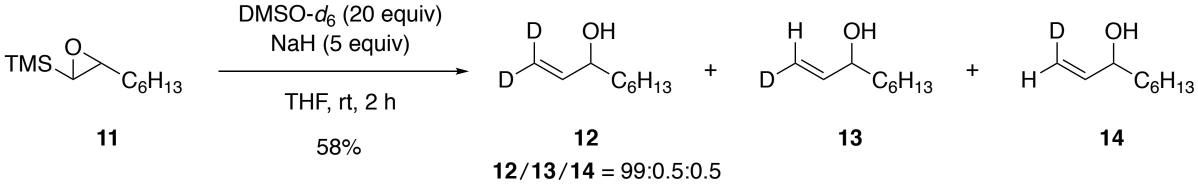
1a/s, indicating no difference in reactivity between the diastereomers. In accordance with the indication, anti isomer **1a**[8] was consumed completely in the same period of time (3 h) to afford anti diol **2a** in 75% yield (entry 2). Similarly, syn isomer **1s**[8] afforded syn diol **2s** (entry 3). A small signals detected in each of the ^{1}H NMR spectra of **2a/s**, **2a**, and **2s** at δ 5.2–5.4 ppm were assigned as hydrogens of **3a/s** and **4a/s** on the basis of the coupling pattern (dd with J = 1.2 Hz for the small doublet):[9] δ 5.32 (dd, J = 17.2, 1.2 Hz) for **3a**; 5.26 (dd, J = 10.3, 1.2 Hz) for **4a**; 5.35 (dd, J = 17.2, 1.2 Hz) for **3s**; 5.23 (dd, J = 10.8, 1.2 Hz) for **4s**. Integration of the signals indicated 96% purity of **2a/s** over **3a/s** and **4a/s**. Since deuteration degree of DMSO-d_6 was >99.96%,[4] a sequence of reactions shown in Scheme 1 is likely to be involved for the production of **3a/s** and **4a/s**. Thus, the D–H exchange between NaDMSO-d_5 (**9**-d_5) and the hydroxyl group of **1a/s** (OH) afforded $CD_3S(O)CD_2H$ (DMSO-d_5) and alkoxide **10a/s**, and a D–D exchange with **9**-d_5 should produce Na^+ $CD_3S(O)CDH^-$ (**9**-d_4). Subsequently, reaction of **10a/s** with **9**-d_4 produced **3a/s** and **4a/s**, whereas the reaction with D-full anion **9**-d_5 afforded **2a/s**.



Scheme 1. Plausible mechanism for the contamination of hydrogen atom

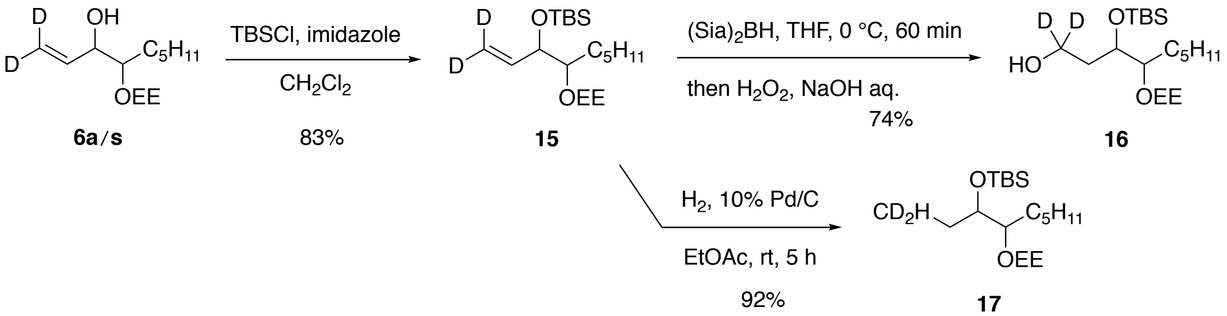
Next, α-ethoxyethyl (EE) ether **5a/s**[8] was subjected to the reaction to afford **6a/s**, which was 98% pure over **7a/s** and **8a/s**. The increased D proportion was consistent with the above hypothesis (Entry 4).

A simple epoxide **11**, prepared by epoxidation of the corresponding olefin with *m*-CPBA in 71% yield, underwent a similar reaction with NaDMSO-d_5 to afford **12** in 58% yield with 99% purity over **13** and **14**.



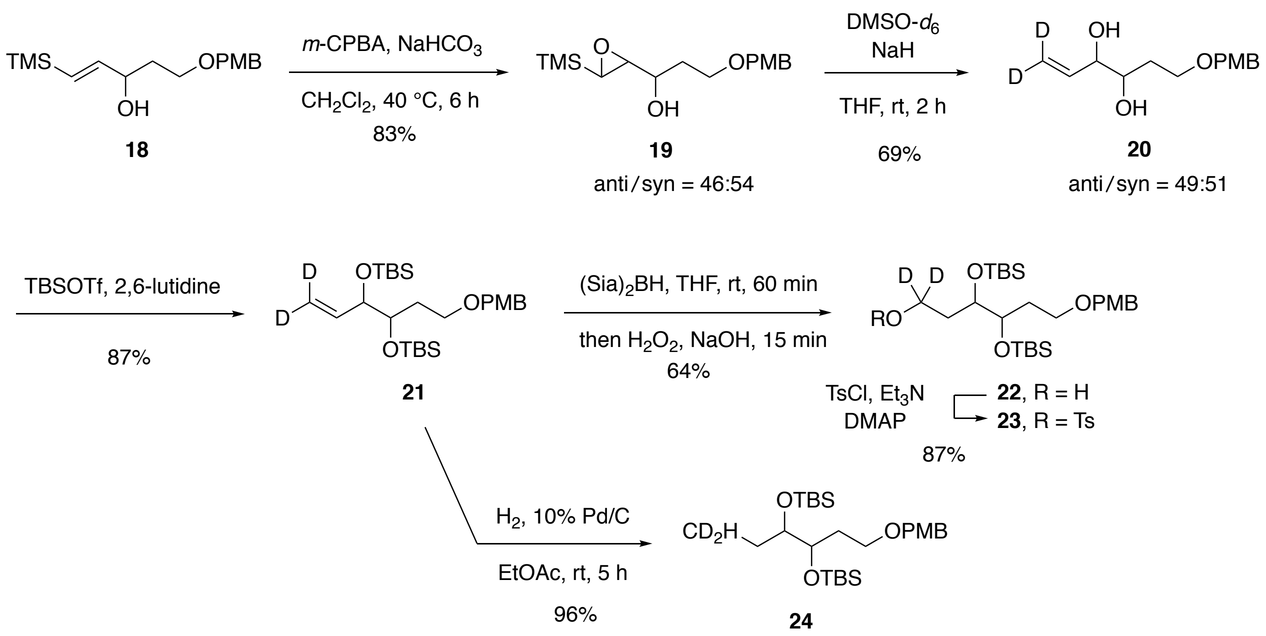
Scheme 2. Reaction of a TMS-epoxide with NaDMSO-d_5

Transformations of **6a/s** were summarized in Scheme 3. Silylation with TBSCl gave **15** in 83% yield. Hydroboration with $(Sia)_2BH$ at 0 °C for 60 min proceeded well and subsequent oxidation with H_2O_2 afforded alcohol **16** in 74% yield. On the other hand, hydrogenation of **15** gave **17** possessing the ethyl-d_2 group in 92% yield.



Scheme 3. Transformation of **6a/s**. TBS: *t*-$BuMe_2Si$, Sia: $Me_2CHCH(Me)$-

Epoxide **19**, prepared as a diastereomeric mixture by epoxidation of allylic alcohol **18**[10] with *m*-CPBA, was the next substrate of the reaction with NaDMSO-d_5, which under similar conditions produced diol **20** in 69% yield (Scheme 4). A diastereomeric ratio of **20** was almost similar to that of epoxide **19**, and the result indicated no difference in reactivity between the anti and syn isomers. For further transformation, diol **20** was converted to bis-TBS ether **21** and subjected to hydroboration with $(Sia)_2BH$, which was slow at 0 °C, but proceeded at rt. After 60 min, completion of the reaction was confirmed by TLC and oxidative work-up afforded alcohol **22** in 64% yield. Subsequent tosylation smoothly gave tosylate **23** in 87% yield. Products **22** and **23** are symmetrical hexyl alcohols possessing four hydroxyl groups, which are properly differentiated, and thus would be versatile intermediates for further transformations to deuterated dihydroxy and epoxy metabolites of polyunsaturated fatty acids.[11] Hydrogenation of olefin **21** gave **24** with the ethyl-d_2 group quantitatively. The product would especially be useful for synthesis of 17,18-diol and 17,18-epoxy derivatives of ω-3 fatty acids such as linolenic acid, EPA, and DHA.[12]



Scheme 4. Transformation of the TMS-epoxy alcohol **19** possessing the PMB-oxy group
m-CPBA: *m*-$ClC_6H_4CO_3H$, PMB: *p*-$MeOC_6H_4CH_2$, DMAP: $Me_2NC_5H_4N$

In summary, we established a new method for incorporation of deuterium using the reaction of 1-TMS-1,2-epoxy-3-alkanols with NaDMSO-d_5.[13] Both anti and syn epoxy alcohols are available[8] and the reaction proceeded without isomerization (Table 1). Hydroboration and hydrogenation were examined as further transformations to afford compounds possessing "CH_2CD_2OH" and "CH_2CD_2H", respectively. As reported previously,[14] these diols and mono-EE protective form would be useful intermediates for synthesis of biologically active diols and epoxides that are produced by cytochrome P450-catalyzed oxidation of polyunsaturated fatty acids.

EXPERIMENTAL

Typical Procedure for the Epoxide Ring Opening. Synthesis of (3*R,4*S**)-Non-1-ene-1,1-*d*$_2$-3,4-diol (2a).** A dispersion of NaH (60 wt% in mineral oil, 120 mg, 3.00 mmol) was washed with dry hexane to remove the oil and added DMSO-d_6 (0.60 mL, 8.48 mmol). The mixture was stirred at 70–75 °C for 45 min and cooled to rt. To the solution was added anti epoxy alcohol **1a** (91 mg, 0.421 mmol) in THF (2 mL). The mixture was stirred at rt for 3 h, cooled to 0 °C, diluted with saturated aqueous NH_4Cl, and extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to give diol **2a** (50 mg, 75%): liquid; R_f 0.37 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3 H), 1.22–1.56 (m, 8 H), 1.96 (br s, 1 H), 2.09 (br s, 1 H), 3.64–3.74 (m, 1 H), 4.07–4.14 (m, 1 H), 5.88–5.95 (m, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 14.1 (+), 22.6 (–), 25.6 (–), 31.8 (–), 32.0 (–), 74.2 (+), 76.0 (+), 117.0 (quint., J = 24 Hz) (–), 135.9 (+); HRMS (FAB$^+$) calcd for $C_9H_{16}D_2O_2Na$ [$(M+Na)^+$] 183.1330, found

183.1333. The ^{13}C and ^{13}C–APT NMR spectra were identical with those reported for the non-deuterated anti diol.[14]

ACKNOWLEDGEMENTS

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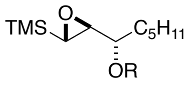
REFERENCES AND NOTES

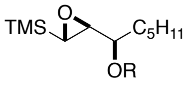
1. (a) J. R. Hanson, 'The Organic Chemistry of Isotopic Labelling', Royal Society of Chemistry, 2011; (b) H. Muchalski, *ARKIVOC*, 2017, **ii**, 507.
2. (a) V. Bizet, X. Pannecoucke, J.-L. Renaud, and D. Cahard, *Angew. Chem. Int. Ed.*, 2012, **51**, 6467; (b) F. Maltais, Y. C. Jung, M. Chen, J. Tanoury, R. B. Perni, N. Mani, L. Laitinen, H. Huang, S. Liao, H. Gao, H. Tsao, E. Block, C. Ma, R. S. Shawgo, C. Town, C. L. Brummel, D. Howe, S. Pazhanisamy, S. Raybuck, M. Namchuk, and Y. L. Bennani, *J. Med. Chem.*, 2009, **52**, 7993; (c) Y. Xiao and P. Liu, *Angew. Chem. Int. Ed.*, 2008, **47**, 9722; (d) H. V. Thulasiram, R. M. Phan, S. B. Rivera, and C. D. Poulter, *J. Org. Chem.*, 2006, **71**, 1739; (e) J. Haesler, I. Schindelholz, E. Riguet, C. G. Bochet, and W. Hug, *Nature*, 2007, **446**, 526; (f) J. M. Concellón, P. L. Bernad, V. del Solar, and J. R. Suárez, *J. Org. Chem.*, 2006, **71**, 6420; (g) M. Miyashita, M. Sasaki, I. Hattori, M. Sakai, and K. Tanino, *Science*, 2004, **305**, 495; (h) J.-L. Abad, G. Fabriás, and F. Camps, *J. Org. Chem.*, 2000, **65**, 8582; (i) L. S. Trzupek, E. R. Stedronsky, and G. M. Whitesides, *J. Org. Chem.*, 1972, **37**, 3300.
3. (a) J. Atzrodt, V. Derdau, W. J. Kerr, and M. Reid, *Angew. Chem. Int. Ed.*, 2018, **57**, 3022; (b) Y. Sawama, K. Park, T. Yamada, and H. Sajiki, *Chem. Pharm. Bull.*, 2018, **66**, 21; (c) W. J. S. Lockley, *J. Labelled Compd. Radiopharm.*, 2007, **50**, 779; (d) A. Rosales and I. Rodríguez-García, *Beilstein J. Org. Chem.*, 2016, **12**, 1585; (e) S. Ma, G. Villa, P. S. Thuy-Boun, A. Homs, and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2014, **53**, 734; (f) L. Neubert, D. Michalik, S. Bähn, S. Imm, H. Neumann, J. Atzrodt, V. Derdau, W. Holla, and M. Beller, *J. Am. Chem. Soc.*, 2012, **134**, 12239; (g) M. Takahashi, K. Oshima, and S. Matsubara, *Chem. Lett.*, 2005, **34**, 192; (h) C. M. Yung, M. B. Skaddan, and R. G. Bergman, *J. Am. Chem. Soc.*, 2004, **126**, 13033; (i) H. Sajiki, F. Aoki, H. Esaki, T. Maegawa, and K. Hirota, *Org. Lett.*, 2004, **6**, 1485; (j) M. B. Skaddan, C. M. Yung, and R. G. Bergman, *Org. Lett.*, 2004, **6**, 11.
4. DMSO-d_6 (deuteration degree minimum 99.96%) in ampoules was purchased from Merck. Each ampoule was freshly opened before use.
5. Y. Kobayashi, T. Ito, I. Yamakawa, H. Urabe, and F. Sato, *Synlett*, 1991, 813.
6. (a) C. R. Lamberson, L. Xu, H. Muchalski, J. R. Montenegro-Burke, V. V. Shmanai, A. V. Bekish, J. A. McLean, C. F. Clarke, M. S. Shchepinov, and N. A. Porter, *J. Am. Chem. Soc.*, 2014, **136**, 838;

(b) C. Oger, V. Bultel-Poncé, A. Guy, L. Balas, J.-C. Rossi, T. Durand, and J.-M. Galano, *Chem. Eur. J.*, 2010, **16**, 13976; (c) S. Peng, C. M. McGinley, and W. A. van der Donk, *Org. Lett.*, 2004, **6**, 349; (d) S. Peng, N. M. Okeley, A.-L. Tsai, G. Wu, R. J. Kulmacz, and W. A. van der Donk, *J. Am. Chem. Soc.*, 2001, **123**, 3609; (e) D. L. Luthria and H. Sprecher, *Lipids*, 1993, **28**, 853; (f) R. Adlof, *J. Labelled Compd. Radiopharm.*, 1990, **28**, 111; (g) B. E. Marron, R. A. Spanevello, M. E. Elisseou, C. N. Serhan, and K. C. Nicolaou, *J. Org. Chem.*, 1989, **54**, 5522.

7. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1345.
8. The mixture of **1a/s** was prepared from the corresponding allylic alcohol by epoxidation with *m*-CPBA, and separated by chromatography on silica gel. Enantioenriched anti isomers such as **1a** are available: Y. Kitano, T. Matsumoto, and F. Sato, *Tetrahedron*, 1988, **44**, 4073, whereas the Mitsunobu inversion affords syn epoxy alcohols. Relative stereochemistry of anti (**a**) and syn (**b**) isomers of **1a/s** and **5a/s** are:

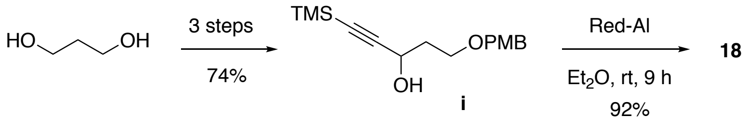


anti isomers **1a**,**5a**



syn isomers **1s**,**5s**

9. The pattern of the hydrogen in the product derived with NaDMSO: dt with $J = 1.2$ Hz for the triplet, indicating couplings with the gem-hydrogen and a hydrogen in a long range distance.
10. Prepared by Red-Al reduction of acetylene **i**, which was, in turn, synthesized from 1,3-propanediol in three steps according to the procedure: N. Ogawa and Y. Kobayashi, *Tetrahedron Lett.*, 2009, **50**, 6079.



11. (a) C. N. Serhan and N. A. Petasis, *Chem. Rev.*, 2011, **111**, 5922; (b) P. Bui, S. Imaizumi, S. R. Beedanagari, S. T. Reddy, and O. Hankinson, *Drug Metab. Dispos.*, 2011, **39**, 180.
12. (a) J. Kunisawa, M. Arita, T. Hayasaka, T. Harada, R. Iwamoto, R. Nagasawa, S. Shikata, T. Nagatake, H. Suzuki, E. Hashimoto, Y. Kurashima, Y. Suzuki, H. Arai, M. Setou, and H. Kiyono, *Sci. Rep.*, 2015, **5**, 9750; (b) G. Zhang, D. Panigrahy, L. M. Mahakian, J. Yang, J.-Y. Liu, K. S. S. Lee, H. I. Wettersten, A. Ulu, X. Hu, S. Tam, S. H. Hwang, E. S. Ingham, M. W. Kieran, R. H. Weiss, K. W. Ferrara, and B. D. Hammock, *Proc. Natl. Acad. Sci. U. S. A.*, 2013, **110**, 6530; (c) J. R. Falck, G. Wallukat, N. Puli, M. Goli, C. Arnold, A. Konkel, M. Rothe, R. Fischer, D. N. Müller, and W.-H. Schunck, *J. Med. Chem.*, 2011, **54**, 4109.
13. Although, yields shown in Table 1 and Scheme 1 were somewhat low, no other by-product(s) was isolated.
14. Y. Nanba, R. Shinohara, M. Morita, and Y. Kobayashi, *Org. Biomol. Chem.*, 2017, **15**, 8614.