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A new and versatile synthesis of 3-substituted oxetan-3-yl methyl alcohols

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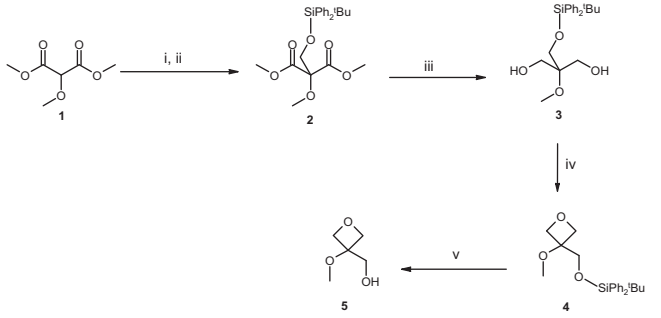
ABSTRACT

We have developed a novel route for the efficient synthesis of pharmaceutically significant 3-substituted oxetan-3-yl methyl alcohols starting from readily available malonates. The synthesis harnesses the diversity of malonate chemistry and allows access to a range of oxetanes, which exemplifies the versatility of this procedure.

Oxetanes are important functional groups for drug discovery[1–3] and since Carreira's pioneering work in 2006,[2] and subsequent publications,[3] interest in oxetanes has been revitalised. Their judicious incorporation into a molecule allows the medicinal chemist the potential to improve metabolic stability whilst maintaining or reducing lipophilicity.[3] The ring oxygen can act as a hydrogen bond acceptor which can lead to increase in potency.[4] They have been used as replacements for *gem*-dimethyl, isopropyl, carbonyl, methylene and *tert*-butyl groups in drug development projects.[3,5] Herein we disclose the preparation of two previously unreported 3-substituted oxetan-3-yl methyl alcohols, which were required as part of a drug discovery project at AstraZeneca. The synthetic route we have developed is flexible and versatile and has been used to make an array of 3,3-disubstituted oxetanes.

The initial required intermediate was (3-methoxyoxetan-3-yl)methanol (**5**). Its synthesis had not been previously reported, therefore a new route was designed (Scheme 1) which used readily available dimethyl 2-methoxymalonate (**1**) as a starting material. The first step was the base-mediated reaction of this malonate with formaldehyde to give the primary alcohol in 98% yield. This was protected using TBDPSCl to give dimethyl 2-[(*tert*-butyldiphenylsilyloxy)methyl]-2-methoxymalonate (**2**) in 84% yield. The silyl protecting group was selected to ease the handling and isolation during subsequent steps. Reduction of the diester with lithium aluminium hydride was unsuccessful, however, reduction with lithium



Scheme 1. Reagents and conditions: (i) H_2CO, $NaHCO_3$, EtOH, H_2O, 98%; (ii) TBDPSCl, imidazole, DMF, 84%; (iii) $LiBH_4$, THF, 80%; (iv) *n*-BuLi, TsCl, THF, then *n*-BuLi, 70%; (v) TBAF, THF, 82%.

borohydride proceeded smoothly to give 2-{[*tert*-butyl(diphenyl)silyl]oxymethyl}-2-methoxypropane-1,3-diol (**3**) in 80% yield. Attempts to cyclise the diol to the desired oxetane failed when NaH and mesyl chloride were used. However, deprotonation with *n*-BuLi, treatment with tosyl chloride to give the mono tosylated product and then a second deprotonation with *n*-BuLi resulted in the intramolecular displacement of the tosyl group, via a 4-*exo*-tet cyclisation, which gave the silyl protected oxetane **4** in 70% yield.[6] Deprotection with TBAF gave the target oxetane **5** in 82% yield.

Further analogues were subsequently prepared. To achieve this we synthesised a benzyl protected oxetane **11** (Scheme 2). Diazo

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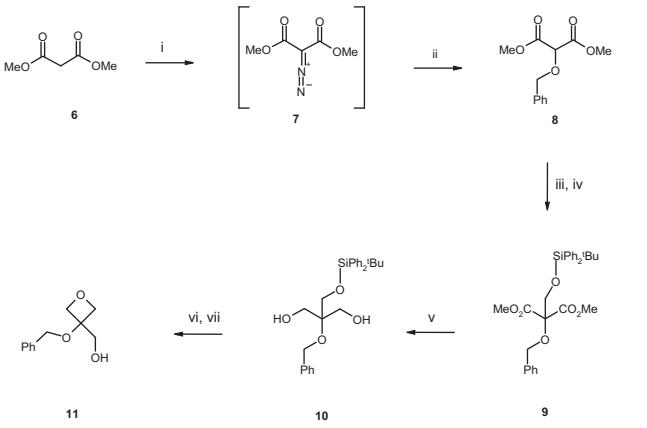
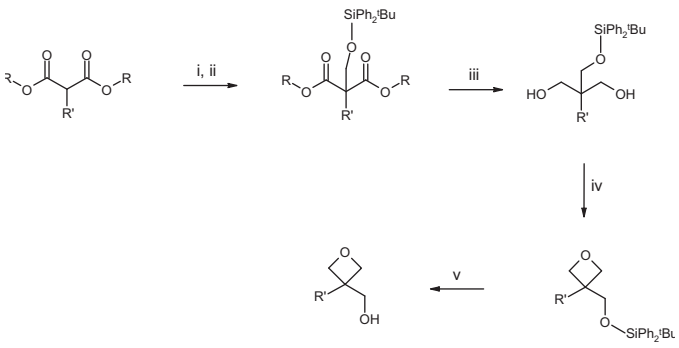


Scheme 2. Reagents and conditions: (i) 4-(Azidosulfonyl)benzoic acid, Et_3N, MeCN; (ii) $Rh(OAc)_2$, $PhCH_2OH$, CH_2Cl_2, 61% (2 steps); (iii) H_2CO, $NaHCO_3$, EtOH, H_2O, 96%; (iv) TBDPSCl, imidazole, DMF, 79%; (v) $LiBH_4$, THF, 77%; (vi) *n*-BuLi, TsCl, THF, then *n*-BuLi, 74%; (vii) TBAF, THF, 82%.

malonate **7** was prepared by the reaction of dimethyl malonate (**6**) with 4-(azidosulfonyl)benzoic acid. This crude diazo material was subjected to a rhodium-catalysed functionalisation to give compound **8** in 61% yield over the two steps.[7] The substituted malonate **8** was converted into the silyl protected alcohol **9**. Subsequent reduction, cyclisation and deprotection gave (3-benzyloxyoxetan-3-yl)methanol (**11**).

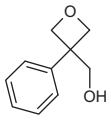
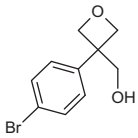
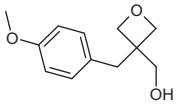
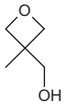
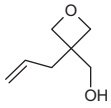
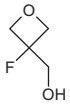
We realised that this synthetic route could be used to synthesise a diverse range of useful oxetane building blocks. A large number of substituted malonates are commercially available and exploitation of the rich variety of malonate chemistry would allow for the incorporation of a wide variety of functional groups at the 3 position of the oxetane products. It is straightforward to introduce an electrophile, an aromatic group or a nucleophile to the central carbon of malonates using well-established technologies.[8] These readily accessible substituted malonates can be used as starting materials. The general route is shown below (Scheme 3). The examples prepared and the yields of each step are displayed in Table 1.

In addition to the 3-oxo-substituted oxetan-3-yl methyl alcohols described in Schemes 1 and 2, the methodology can deliver aromatic and benzyl 3-substituted oxetan-3-yl methyl alcohols (Table 1, entries 1–3). It is also tolerant of methyl, allyl and fluoro substitution of the malonate starting material (Table 1, entries 4–6). We wanted to use this methodology to prepare oxetanes with a nitrogen substituent at the 3 position. Unfortunately, dimethyl 2-nitromalonate and dimethyl 2-(dimethylamino)malonate did not give the desired product in the reaction with formaldehyde.



Scheme 3. Reagents: (i) H_2CO, $NaHCO_3$, EtOH, H_2O; (ii) TBDPSCl, imidazole, DMF; (iii) $LiBH_4$, THF; (iv) *n*-BuLi, TsCl, THF, then *n*-BuLi; (v) TBAF, THF.

Table 1
3,3-Disubstituted oxetanes prepared

Entry	Product	Yield for steps in Scheme 3 (%)				
		i	ii	iii	iv	v
1		58	56	21	87	91
2		56	100	10	78	47
3		91	85	67	62	72
4		100	56	84	59	84
5		99	74	43	66	85
6		72	55	79	66	83

In summary, we have discovered and developed a new synthetic route, which has been used to synthesise two examples of previously unreported 3-*O*-substituted oxetan-3-yl methyl alcohols. These oxetanes are synthetically useful and can be diversified further as required. They have been used to construct active target compounds for a number of our drug discovery projects. We have demonstrated the flexibility of this approach by applying it to the preparation of a diverse range of synthetically useful oxetane building blocks.

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Supplementary data

Supplementary data (experimental and compound characterisation) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.06.024.

References and notes

1. (a) Edward, J. T.; Farrell, P. G.; Shahidi, F. J. *Chem. Soc. Faraday Trans.* **1977**, *73*, 705; (b) Wang, M.; Cornett, B.; Nettles, J.; Liotta, D. C.; Snyder, J. P. *J. Org. Chem.* **2000**, *65*, 1059; (c) Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, A.; Takita, T. *J. Antibiot.* **1986**, *39*, 1623.
2. Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7736.
3. (a) Wuitschik, G.; Rogers-Evans, M.; Buckl, A.; Bernasconi, M.; Märki, M.; Godel, T.; Fischer, H.; Wagner, B.; Parrilla, I.; Schuler, F.; Schneider, J.; Alker, A.; Schweizer, W. B.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4512; (b) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. *J. Med. Chem.* **2010**, *53*, 3227; (c) Burkhard, J. A.;

Wuitschik, G.; Plancher, J.-M.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett.* **2013**, *15*, 4312.
4. (a) Berthelot, M.; Besseau, F.; Laurence, C. *Eur. J. Org. Chem.* **1998**, 925; (b) Besseau, F.; LuJon, M.; Laurence, C.; Berthelot, M. *J. Chem. Soc., Perkin Trans. 2* **1998**, 101.
5. (a) Barnes-Seeman, D.; Jain, M.; Bell, L.; Ferreira, S.; Cohen, S.; Chen, X.-H.; Amin, J.; Snodgrass, B.; Hatsis, P. *Med. Chem. Lett.* **2013**, *4*, 514; (b) Toshie, F.; Takato, N.; Tsutomu, S. *Bioorg. Med. Chem.* **2013**, *21*, 5209; (c) Dowling, J. E.; Alimzhanov, M.; Bao, L.; Block, M. H.; Chuaqui, C.; Cooke, E. L.; Denz, C. R.; Hird, A.; Huang, S.; Larsen, N. A. *Med. Chem. Lett.* **2013**, *4*, 800; (d) Gentry, P. R.; Bridges, T. M.; Lamsal, A.; Vinson, P. N.; Smith, E.; Chase, P.; Hodder, P. S.; Engers, J. L.; Niswender, C. M.; Scott Daniels, J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2996.
6. Picard, P.; Leclercq, D.; Bats, J.-P.; Moulines, J. *Synthesis* **1981**, *7*, 550.
7. Shevchenko, V. V.; Zhegalova, N. G.; Borzenko, A. O.; Nikolaev, V. A. *Helv. Chim. Acta* **2008**, *91*, 501.
8. (a) Gomtsyan, A.; Didomenico, S.; Lee, C.-H.; Matulenko, M. A.; Kim, K.; Kowaluk, E. A.; Wismer, C. T.; Mikusa, J.; Yu, H.; Kohlhaas, K.; Jarvis, M. F.; Bhagwat, S. S. *J. Med. Chem.* **2002**, *45*, 3639; (b) Fracchiolla, G.; Laghezza, A.; Piemontese, L.; Parente, M.; Carbonara, G.; Tortorella, P.; Loiodice, F.; Lavecchia, A.; Di Giovanni, C.; Novellino, E.; Pochetti, G.; Montanari, R. *Bioorg. Med. Chem.* **2012**, *20*, 2141; (c) Ward, R. A.; Brassington, C.; Breeze, A. L.; Caputo, A.; Critchlow, S.; Davies, G.; Goodwin, L.; Hassall, G.; Greenwood, R.; Holdgate, G. A.; Mrosek, M.; Norman, R. A.; Pearson, S.; Tart, J.; Tucker, J. A.; Vogtherr, M.; Whittaker, D.; Wingfield, J.; Winter, J.; Hudson, K. *J. Med. Chem.* **2012**, *55*, 3285; (d) Yoshida, M.; Maeyama, Y.; Shishido, K. *Tetrahedron* **2012**, *68*, 9962; (e) Donald, C.; Boyd, S. *Tetrahedron Lett.* **2012**, *53*, 3853; (f) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473; (g) Sebesta, R.; Skvorcova, A. *J. Organomet. Chem.* **2009**, *694*, 1898; (h) Yip, K.-T.; Zhu, N.-Y.; Yang, D. *Org. Lett.* **2009**, *11*, 1911; (i) Peng, B.; Zhang, S.; Yu, X.; Feng, X.; Bao, M. *Org. Lett.* **2011**, *13*, 5402.