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Oxetanes from the Ring Contraction of α-Triflates of γ-Lactones: Oxetane Nucleosides and Oxetane Amino Acids

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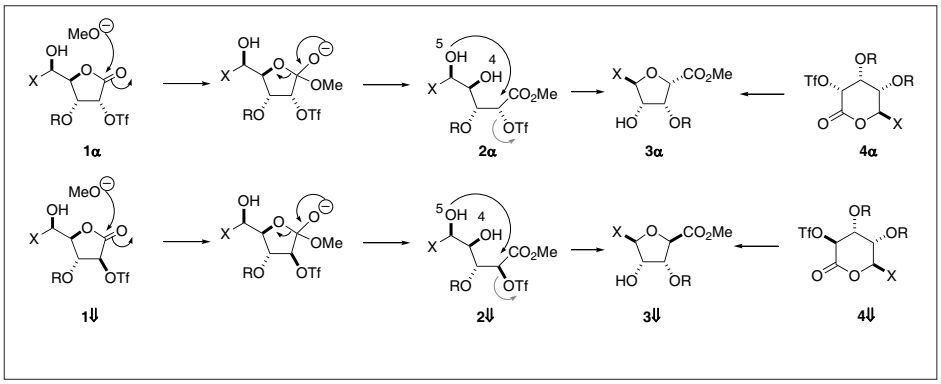
Abstract: α-Triflates of γ-lactones with potassium carbonate in methanol give efficient contraction of the ring to oxetane-1-carboxylates in which the oxygen substituent at C(3) of the oxetane is predominantly *trans* to the carboxylate at C(2), regardless of the stereochemistry of the starting triflate. The limitations of the procedure are discussed and compared with analogous reactions for the preparation of THF carboxylates. The potential of the contraction in the preparation of oxetane nucleosides (such as oxetanocin) and oxetane sugar amino acids (analogues of oxetin) as peptidomimetics with predisposition to form secondary structural motifs is illustrated.

Keywords: Lactones · Nucleoside · Oxetane · Oxetanocin · Oxetin · Ring contraction · Sugar amino acid

1. Ring Contraction of α-Triflates of γ-Lactones to Oxetanes

Acidic or basic methanol treatment of α-triflates of γ-lactones[1] with a free hydroxyl group at C(5) provides a general and high yielding synthesis of highly substituted and homochiral THF carboxylates in which the ring closure occurs with exclusive inversion of configuration at C(2) (Scheme 1).[2] Thus the lactone triflate **1**α undergoes ring opening by methanol/methoxide to form an open chain triflate **2**α which undergoes attack by the C(5)-hydroxyl group to give a clean S_N2 reaction to give **3**α only arising from inversion of configuration at C(2). Although both C(4)- and C(5)-OH groups are free in the open chain triflate **2**α, only the THF ring is formed; there is no oxetane formation by attack from the C(4)-OH group.[3] The epimeric triflate **1**β proceeds in the same stereospecific manner to give exclusively the epimer **3**β. Similarly six-membered rings are formed in favor of oxetanes.[4] The epimeric α-triflates of δ-lactones **4**α and **4**β also give stereospecific conversion to the THF carboxylates **3**α and **3**β, respectively.[5]



Scheme 1. Formation of THF by acid- or base-catalyzed ring contraction of lactone triflates.

In contrast, fully protected α-triflates of γ-lactones with basic methanol give oxetane carboxylates.[6–12] Investigation of the stereochemical outcome of such ring contraction reactions revealed that the predominant, and sometimes exclusive, isomer formed had the carboxylate and the C(3)-oxygen substituent *trans* to each other, regardless of the stereochemistry of the initial triflate (Scheme 2). Thus treatment of either of the epimeric lactones **5**α or **5**β with potassium carbonate in methanol produced the *same* oxetane **7**β as the major product; only a minor – but different – amount of **7**α was formed. Equilibration experiments indicated that the product esters **7** were configurationally stable to the reaction conditions. The S_N2 closure of the open chain triflates **6** to produce the oxetane ring **7** is particularly difficult with a β-oxygen substituent. Thus, epimerization of **6**α to **6**β (with closure to the oxetane **7**β) is faster than the S_N2 formation of the oxetane with the steric hindrance of adjacent *cis*-substituents. For example, the epimeric triflates **8**β and **8**α both give **9**α as the major product with minor – but differing – amounts of the all *cis*-substituted oxetane **9**β (Scheme 3).[7]

Similar ring contractions were observed for all four of the diastereomeric 3,5-di-*O*-benzyl-2-*O*-triflate pentonolactones;[8] all the carboxylates were found to have the C(2) and C(3) substituents on the oxetane ring *trans* to each other (Scheme 4). In contrast to these findings, ring contractions of γ-lactones without oxygen substituents at C(3) were found to proceed with a clean inversion of configuration at C(2) of the sugar lactone; the lack of a β-oxygen substituent may make the S_N2 ring closure easier and competes with epimerization of the open chain triflates.[9]

3-Azido- **10** and 3-fluoro- **12** α-triflates of γ-lactones with potassium carbonate in methanol do not give the corresponding azido- **14** and fluoro- **15** substituted ox-

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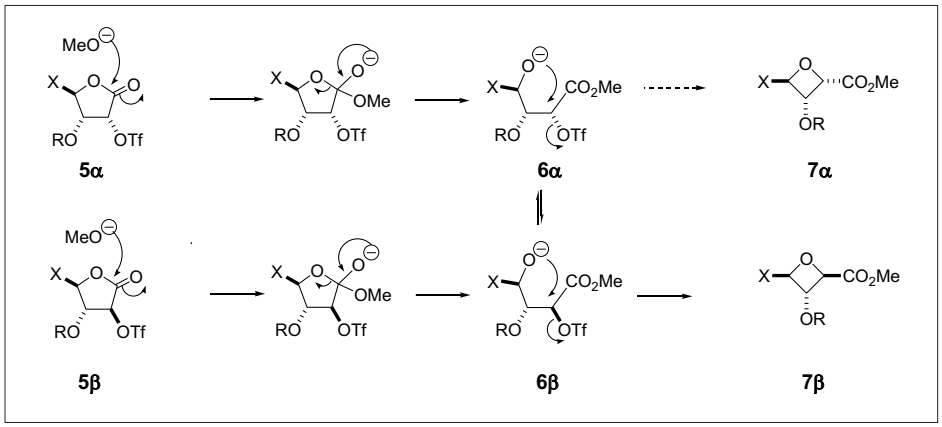
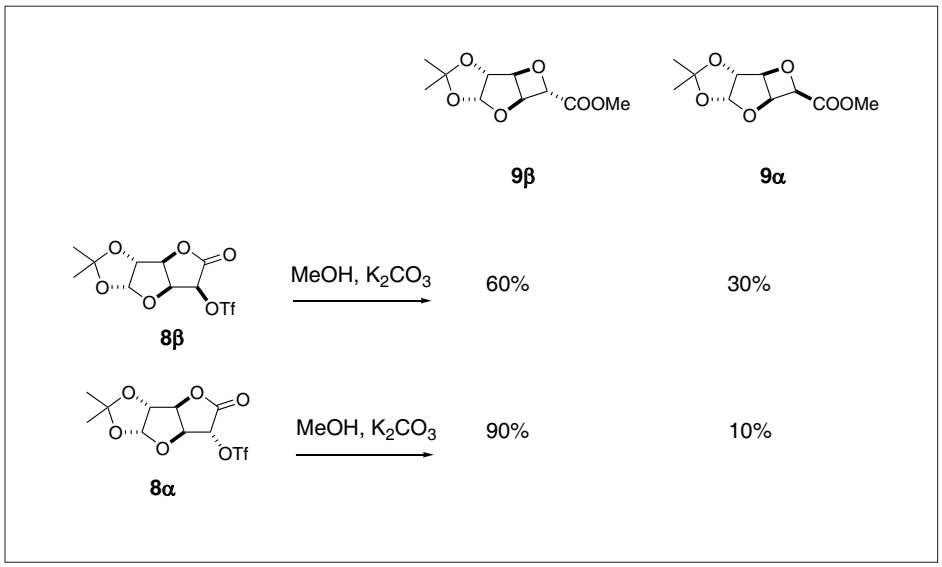
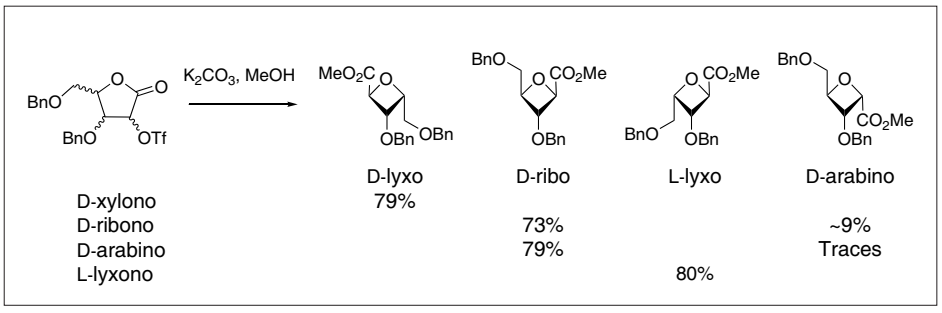


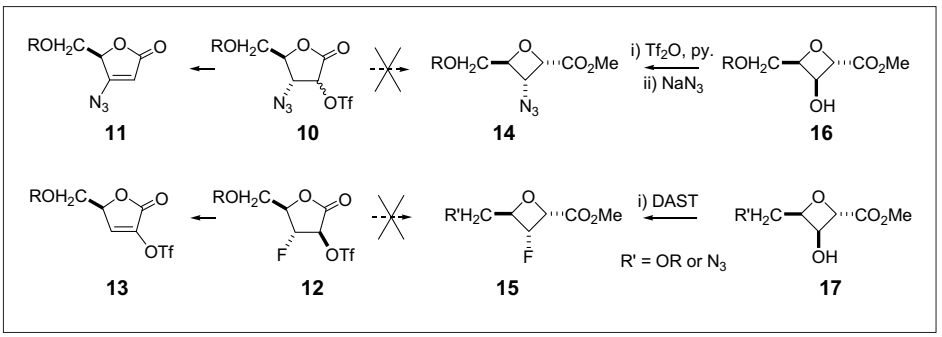
Scheme 2. Formation of oxetanes by ring contraction of γ-lactone triflates.



Scheme 3. Oxetane formation from ring-fused lactones.



Scheme 4. Ring contractions of di-*O*-benzyl-α-triflates of γ-lactones.



Scheme 5. C(3)-substituted fluoro- and azido-oxetanes.

etanes; competing elimination reactions[10] cause loss of triflic acid from the azido triflate **10** to form the azide **11**, whereas the fluoro lactone **12** loses HF to form the vinyl triflate **13** (Scheme 5). However, the azido- **14** and fluoro- **15** oxetanes may be accessed by nucleophilic displacement reactions on the oxetane ring of **16** and **17**, respectively.[11–13] It is remarkable that the β-triflate undergoes a clean high yield S_N2 reaction; presumably the elimination reaction to introduce two sp^2 carbons in the oxetane ring would induce too much strain.

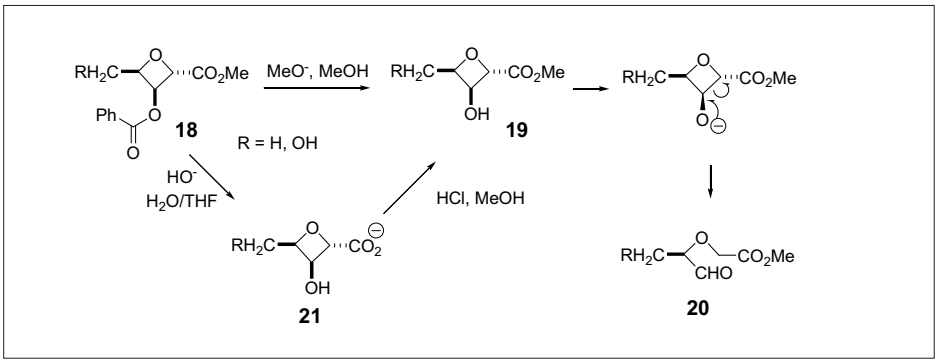
3-Hydroxy oxetane carboxylates are prone to base-catalyzed retro-aldol ring opening. Thus, reaction of the benzoate **18** with basic methanol results in the formation of retro-aldol product **20** (Scheme 6) since the initially formed β-hydroxy ester **19** can readily fragment. Hydrolysis of **18** with hydroxide in aqueous THF – with hydrolysis of the more reactive methyl ester to the carboxylate salt – gives an intermediate **21** which can no longer undergo the retro-aldol reaction.[6,14,15]

A change in the stereochemistry of an oxetane ring *cis*-fused to a benzylidene ring may cause a change in the conformational/configurational preference of the molecule. The rhamnose-derived lactone triflate **22** affords **23** in which the formation of the oxetane occurs with overall retention of configuration at C(2) of the sugar moiety. The epimeric triflate **25** changed the stereochemistry at the benzylidene position on silica to form the triflate **26**. Thus treatment of the mixture of **25** and **26** with potassium carbonate in methanol produced the epimeric benzylidene oxetanes **23** and **27**, both of which on hydrolysis gave the same oxetane **24** (Scheme 7).[16]

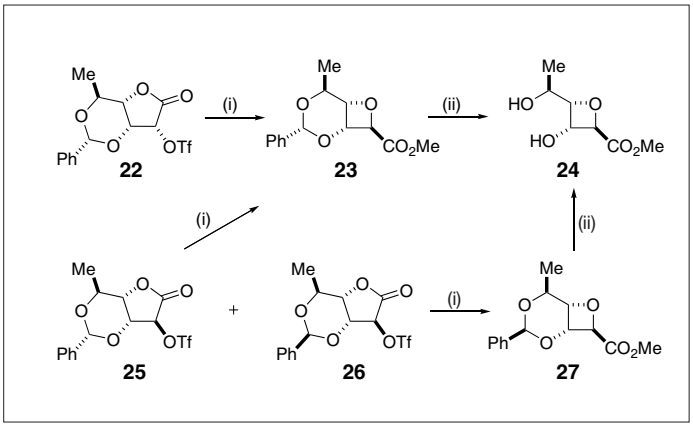
2. Oxetane Nucleosides

Oxetane carboxylates can be transformed by the Barton modification of the Hunsdiecker reaction[17] to stable chlorooxetanes; thus **9** may be converted to **28** (Scheme 8). Chlorooxetanes are much more stable – particularly with a β-oxygen substituent in the oxetane ring – than their furanoside analogues, as S_N1 loss of chloride to produce an sp^2 carbon in a four-membered ring is unfavorable.[18] Reaction of the stable chlorooxetane **28** with a nucleoside base, such as adenine, gives an entry to oxetane nucleosides **29** (Scheme 8).[19]

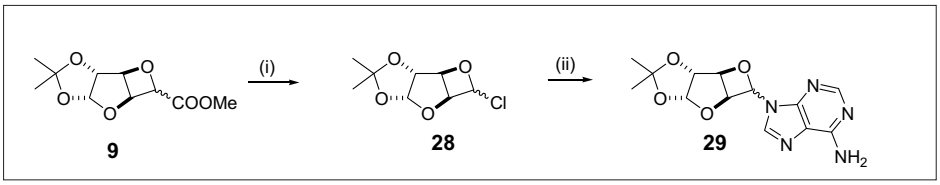
Two oxetane nucleosides have been isolated as natural products. Albucidin **30**,[20] a novel herbicide from the culture broth of *Streptomyces albus*, has an activity against HIV approximately 10-fold that of oxetanocin A (**31**), isolated from *Bacillus megaterium*.[21] Oxetanocin **31** was prepared (Scheme 9) from the lactone triflate **34**, itself derived from diacetone glu-



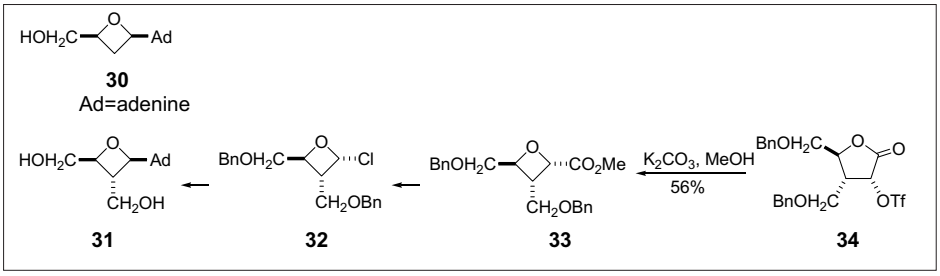
Scheme 6. Retro-aldol condensation of 3-hydroxy oxetane carboxylates.



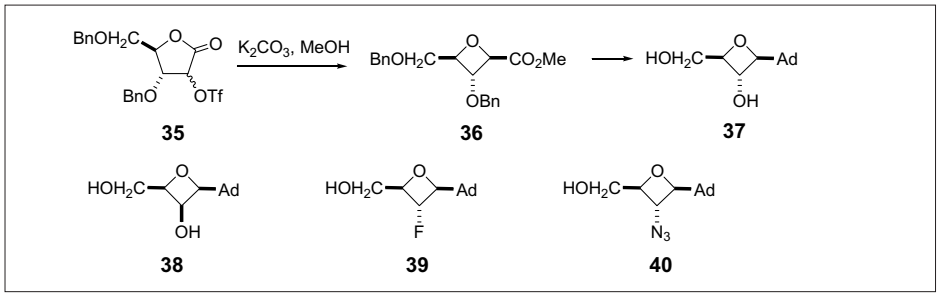
Scheme 7. (i) K_2CO_3, MeOH; (ii) HCl, MeOH



Scheme 8. (i) aq. NaOH; then $(COCl)_2$; then *N*-hydroxypyridine-2-thione, CCl_4 (ii) adenine, K_2CO_3, 18-crown-6, MeCN / DMF (1:1).



Scheme 9. Synthesis of oxetanocin.



Scheme 10. Oxetane nucleosides.

cose.[22] Lactone **34**, with a carbon – rather than an oxygen – substituent at C(3), underwent ring contraction to the oxetane with inversion to give **33** in which the carboxylate is *cis* to the adjacent hydroxymethyl substituent. Subsequent conversion to the chloride **32** (less stable since there is no β-oxygen), followed by treatment with adenine, afforded oxetanocin **31**.

Ring contraction of either of the epimeric triflates **35** gave **36** as a key intermediate in the synthesis of oxetanocin analogues, including noroxetanocin **37**, epinoroxetanocin **38**, and the fluoro **39** and azido **40** oxetane nucleosides; epinoroxetanocin **38** was more active against HIV than oxetanocin itself (Scheme 10).[23]

3. Oxetane Amino Acids

Sugar amino acids (SAA) have provided a family of peptidomimetic scaffolds[24] with the propensity to induce secondary structural motifs and with the potential of adjusting properties of the oligopeptides such as solubility and stability to peptide cleavage. The four-membered oxetane rings, being conformationally less flexible than their furanose and pyranose counterparts, provide a class of foldamers with access to a wide range of novel secondary structures. The ring contraction reaction generates oxetane carboxylates which allow conversion to α, β and δ oxetane amino acid scaffolds.

3.1 *Oxetane α-Amino Acids*

Bromination at the α-position of furanose carboxylates to form α-bromoesters, followed by reaction with sodium azide, gives α-azido carboxylates,[25] which can act as α,α-disubstituted THF α-amino acid scaffolds.[26] Similar methodology may be applied to oxetanes; thus, reaction of either of the epimers **9** with LiHMDS followed by CBr_4 gave a separable mixture of the bromides **41** and **42**. Both α-bromoesters **41** and **42** readily underwent displacement with azide with complete inversion of configuration to generate the esters **43** and **44** respectively as oxetane α-amino acid scaffolds (Scheme 11).[27]

3.2 *Oxetane β-Amino Acids*

Oxetin **45**[28] is a naturally occurring antibiotic comprising a *cis*-β-amino acid containing an oxetane ring. Its three stereoisomers do not exhibit antibacterial activity.[29] β-Amino acids are among the most successful families of foldamers, and induce secondary structure – particularly helical motifs – in much shorter sequences than those of α-amino acids.[30] A series of oxetane β-amino acid scaffolds have been prepared as analogues of oxetin **45** and as potential foldamers. Several differ-

ently protected *cis* and *trans*-β-amino acid oligomers have been synthesized from the corresponding β-azido ester monomer units; the key steps in the syntheses are the efficient and high yield S_N2 reactions on triflates β to the carboxylates.[31] The benzylidene triflate **46**, readily available from D-xylose, gives efficient ring contraction to the protected oxetane **47** which may be converted to a number of derivatives **48** with only the secondary OH at C(3) unprotected (Scheme 12). Esterification of **48** by triflic anhydride, followed by S_N2 reaction with cesium trifluoroacetate, gives the epimeric alcohol **49** in over 90% yield. S_N2 displacement of the triflates of **48** and **49** with sodium azide gives high yields of the inverted azides **50** and **51**, respectively. Such azidoesters are ideal intermediates for incorporation of such β-amino acids into oligopeptides.

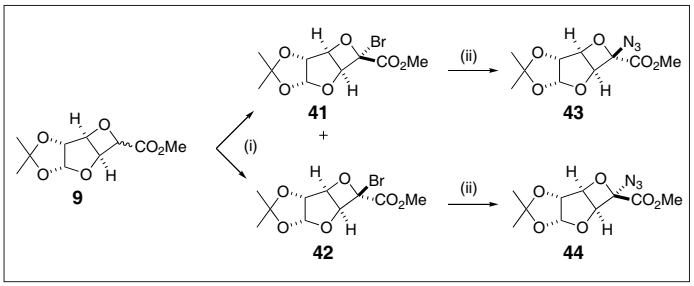
Homooligomers from *cis*-β-amino acids were found to adopt helical conformations in solution stabilized by ten-membered ring hydrogen bonds, with those derived from D-xylose adopting a right-handed – and those from L-rhamnose a left-handed – helical structure. The *trans*-oligomers in contrast formed extended structures in solution stabilized by weak hydrogen bonds.

3.3 *Oxetane* δ*-Amino Acids*

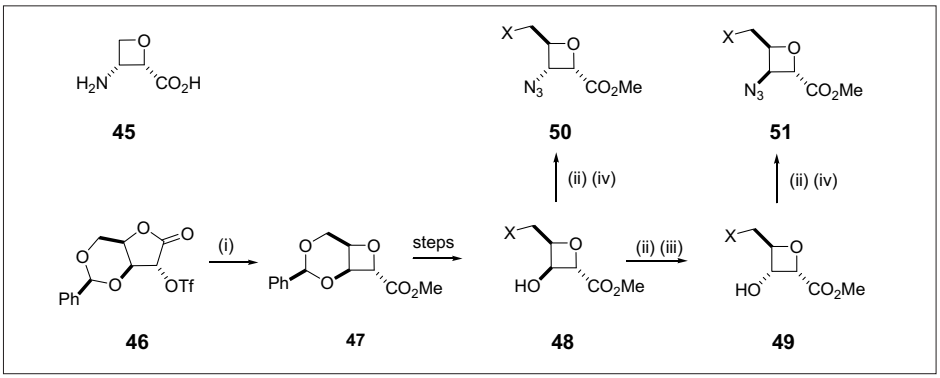
Oxetane δ-amino acids – like their THF and tetrahydropyran congeners – may be viewed as dipeptide isosteres. The side chain azide can be introduced before or after the ring contraction of the lactone. The value of the Hanessian reaction[32] for introduction of the azide after formation of the oxetane is illustrated in the synthesis of 2,4-*trans* δ-azido ester monomer units (Scheme 13). The benzylidene oxetanes **47** (from D-xylose) and **27** (from L-rhamnose) react with *N*-bromosuccinimide (NBS) to give the bromides **52** and **54** respectively; the bromides can readily be manipulated to give the corresponding azides **53** and **55**.[33]

For 2,4-*cis* δ-azido ester monomers, introduction of the azide prior to oxetane formation is generally preferable in order to avoid intermediates that can undergo reverse aldol reactions (Scheme 14). Thus the triflates **56** (from L-arabinose) and **57** (from L-xylose) afford the oxetanes **58** and **59**, respectively.[6,13–15]

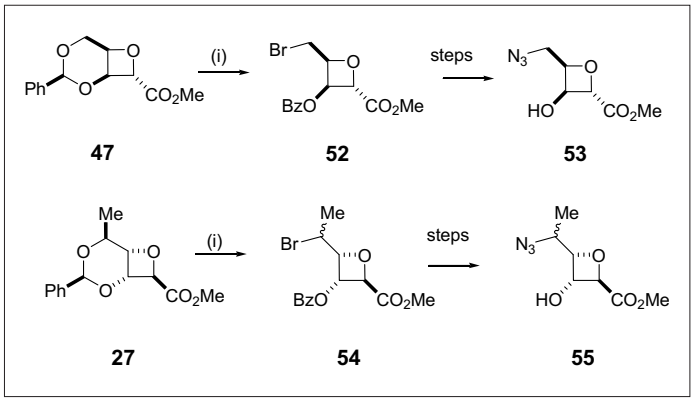
The 2,4-*cis*-oxetane δ-amino acid scaffold derived from **58** formed a repeating β-turn type structure, whereas oligomers of the 2,4-*trans*-oxetane δ-amino acid scaffolds derived from **53** and **55** did not adopt well-defined secondary structures stabilized by hydrogen bonding.[34] A cyclic tetramer **61** is formed by hydrogenation of a linear azido-pentafluorophenyl ester tetramer **60** at high dilution (Scheme 15).[35]



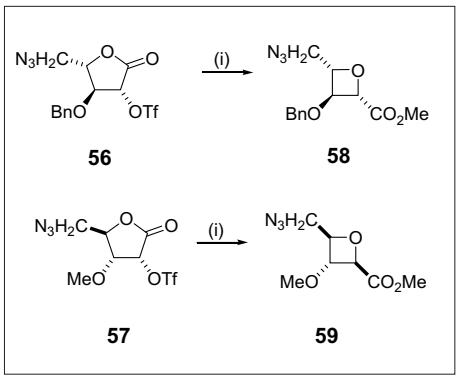
Scheme 11. (i) LiHMDS, THF, –78 °C; then CBr_4 (ii) NaN_3, DMF, RT.



Scheme 12. (i) K_2CO_3 MeOH (ii) Tf_2O, pyridine, CH_2Cl_2 –30 to –20°C (iii) $CsOCOCF_3$, MeCOEt (iv) NaN_3, DMF.



Scheme 13. (i) NBS, $BaCO_3$, CCl_4.



Scheme 14. (i) K_2CO_3, MeOH.

4. Summary

Oxetane carboxylic acids can be readily synthesized by the ring contraction of α-triflates of γ-lactones with basic methanol, provided that the oxygen substituent at C(3) is *trans* to the carboxylate. This method has been applied to the synthesis of oxetane nucleosides and a range of oxetane sugar amino acid scaffolds with a predisposition towards the formation of secondary structural features in small oligomers.

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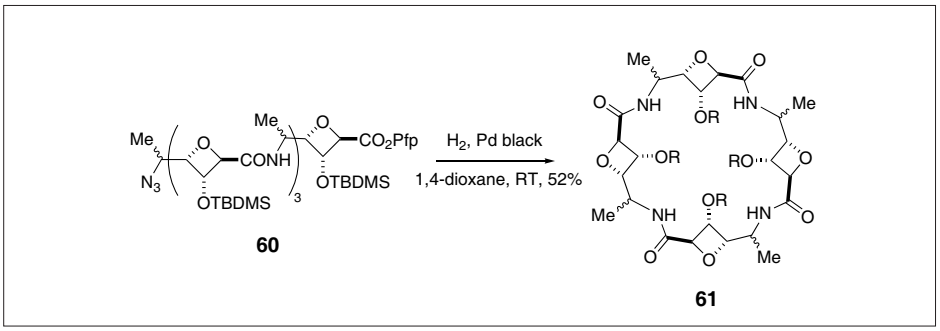
[1] J. R. Wheatley, C. J. F. Bichard, S. J. Mantell, J. C. Son, D. J. Hughes, G. W. J. Fleet, D. Brown, *J .Chem. Soc., Chem. Commun.* **1993**, 1065.
[2] a) A. A. Edwards, G. J. Sanjayan, S. Hachisu, R. Soengas, A. Stewart, G. E. Tranter, G. W. J. Fleet, *Tetrahedron* **2006**, *62*, 4110; b) G. J. Sanjayan, A. Stewart, S. Hachisu, R. Gonzalez, M. P. Watterson, G. W. J. Fleet, *Tetrahedron Lett.* **2003**, *44,* 5847; c) M. P. Watterson, A. A. Edwards, J. A. Leach, M. D. Smith, O. Ichihara, G. W. J. Fleet, *Tetrahedron Lett.* **2003**, *44*, 5853.
[3] R. Csuk, E. Prell, *Tetrahedron* **2010**, *66*, 1313.
[4] a) J. C. Estevez, A. J. Fairbanks, G. W. J. Fleet, *Tetrahedron* **1998**, *54*, 13591; b) K. Y. Hsia, P. Ward, G. W. J. Fleet, *Tetrahedron Lett.* **1994**, *35*, 3361.
[5] S. S. Choi, P. M. Myerscough, A. J. Fairbanks, B. M. Skead, C. J. F. Bichard, S. J. Mantell, G. W. J. Fleet, J. Saunders, D. Brown, *J. Chem. Soc., Chem. Commun.* **1992**, 1605.
[6] B. Lopez-Ortega, S. F. Jenkinson, T. D. W. Claridge, G. W. J. Fleet, *Tetrahedron: Asymm.* **2008**, *19*, 976.



Scheme 15. Formation of cyclic tetramer.

[7] G. N. Austin, G. W. J. Fleet, J. M. Peach, K. Prout, J. C. Son, *Tetrahedron Lett.* **1987**, *28*, 4741.

[8] D. R. Witty, G. W. J. Fleet, K. Vogt, F. X. Wilson, Y. Wang, R. Storer, P. L. Myers, C. J. Wallis, *Tetrahedron Lett.* **1990**, *31*, 4787.

[9] D. R. Witty, G. W. J. Fleet, S. Choi, K. Vogt, F. X. Wilson, Y. Wang, R. Storer, P. L. Myers, C. J. Wallis, *Tetrahedron Lett.* **1990**, *31*, 6927.

[10] R. P. Elliott, G. W. J. Fleet, K. Vogt, F. X. Wilson, Y. Wang, D. R. Witty, R. Storer, P. L. Myers, C. J. Wallis, *Tetrahedron: Asymm.* **1990**, *1*, 715.

[11] Y. Wang, G. W. J. Fleet, F. X. Wilson, R. Storer, P. L. Myers, C. J. Wallis, O. Doherty, D. J. Watkin, K. Vogt, D. R. Witty, J. M. Peach, *Tetrahedron Lett.* **1991**, *32*, 1675.

[12] S. F. Barker, D. Angus, C. Taillefumier, M. R. Probert, D. J. Watkin, M. P. Watterson, T. D. W. Claridge, G. W. J. Fleet, *Tetrahedron Lett*. **2001**, *42*, 4247.

[13] S. D. Lucas, A. P. Rauter, J. Schneider, H. P. Wessel, *J. Carbohydr. Chem*. **2009**, *28*, 431.

[14] a) S. D. Lucas, A. P. Rauter, H. P. Wessel, *J. Carbohydr. Chem*. **2008**, *27*, 172; b) S. D. Lucas, H. Iding, A. Alker, H. P. Wessel, A. P. Rauter, *J. Carbohydr. Chem.* **2006**, *25*,187.

[15] S. F. Jenkinson (née Barker), T. Harris, G. W. J. Fleet, *Tetrahedron: Asymm.* **2004**, *15*, 2667.

[16] S. W. Johnson, D. Angus, C. Taillefumier, J. H. Jones, D. J. Watkin, E. Floyd, J. G. Buchanan, G. W. J. Fleet, *Tetrahedron: Asymm.* **2000**, *11*, 4113.

[17] D. H. R. Barton, D. Crich, W. B. Motherwell, *Tetrahedron* **1985**, *41*, 3901.

[18] G. W. J. Fleet, J. C. Son, J. M. Peach, T. A. Hamor, *Tetrahedron Lett.* **1988**, *29*, 1449.

[19] G. W. J. Fleet, J. C. Son, K. Vogt, J. M. Peach, T. A. Hamor, *Tetrahedron Lett.* **1988**, *29*, 1451.

[20] a) D. R. Hahn, P. R. Graupner, E. Chapin, J. Gray, D. Heim, J. R. Gilbert, B. C. Gerwick, *J. Antibiot.* **2009**, *62*, 191; b) M. Kitagawa, S. Hasegawa, S. Saito, N. Shimada, T. Takita, *Tetrahedron Lett.* **1991**, *32*, 3531.

[21] a) N. Shimada, S. Hasegawa, T. Harada, T. Tomisawa, A. Fujii, T. Takita, *J. Antibiot.* **1986**, *39*, 1623; b) A. Rustullet, R. Alibes, P. de March, M. Figueredo, J. Font, *Org. Lett.* **2007**, *15*, 2827.

[22] F. X. Wilson, G. W. J. Fleet, K. Vogt, Y. Wang, D. R. Witty, R. Storer, P. L. Myers, C. J. Wallis, *Tetrahedron Lett.* **1990**, *31*, 6931.

[23] a) F. X. Wilson, G. W. J. Fleet, D. R. Witty, K. Vogt, Y. Wang, R. Storer, P. L. Myers, C. J. Wallis, *Tetrahedron: Asymm.* **1990**, *1*, 525; b) Y. Wang, G. W. J. Fleet, R. Storer, P. L. Myers, C. J. Wallis, O. Doherty, D. J. Watkin, K. Vogt, D. R. Witty, F. X. Wilson, J. M. Peach, *Tetrahedron: Asymm.* **1997**, *8*, 527.

[24] a) M. D. P. Risseeuw, M. Overhand, G. W. J. Fleet, M. I. Simone, *Tetrahedron: Asymm.* **2007**, *18*, 2001; b) M. D. Smith, G. W. J. Fleet, *J. Peptide Sci.* **1999**, *5*, 425; c) A. A. Edwards, G. W. J. Fleet, G. E. Tranter, *Chirality* **2006**, *18*, 265.

[25] a) A. J. Fairbanks, G. W. J. Fleet, *Tetrahedron* **1995**, *51*, 3881; b) A. J. Fairbanks, P. S. Ford, D. J. Watkin, G. W. J. Fleet, *Tetrahedron Lett.* **1993**, *34*, 3327.

[26] a) J. C. Estevez, M. D. Smith, M. R. Wormald, G. S. Besra, P. J. Brennan, R. J. Nash, G. W. J. Fleet, *Tetrahedron Asymm.* **1996**, *7*, 391; b) J. C. Estevez, M. D. Smith, A. L. Lane, S. Crook, D. J. Watkin, G. S. Besra, P. J. Brennan, R. J. Nash, G. W. J. Fleet, *Tetrahedron Asymm.* **1996**, *7*, 387.

[27] S. Choi, D. R. Witty, G. W. J. Fleet, P. L. Myers, R. Storer, C. J. Wallis, D. Watkin, L. Pearce, *Tetrahedron Lett.* **1991**, *32*, 3569.

[28] a) S. Omura, M. Murata, N. Imamura, Y. Iwai, H. Tanaka, *J. Antibiot.* **1984**, *31*, 1324; b) M. L. Blauvelt, A. R. Howell, *J. Org. Chem*. **2008**, *73*, 517.

[29] Y. Kawahata, S. Takatsuto, N. Ikekawa, M. Murata, S. Omura, *Chem. Pharm. Bull.* **1986**, *34*, 3102.

[30] a) R. Threlfall, A. Davies, N. M. Howarth, J. Fisher, R. Cosstick, *Chem. Commun.* **2008**, 585; b) D. Seebach, A. K. Beck, D. J. Bierbaum, *Chem. Biodiversity* **2004**, *1*, 1111; c) F. Sussman, M. C. Villaverde, J. C. Estevez, R. J. Estevez, *J. Phys., Chem. B* **2009**, *113,* 9669; d) Y. D. Wu, W. Han, D. P. Wang, Y. Gao, Y. L. Zhao, *Accts. Chem. Res.* **2008**, *41*, 1418; e) P. Schramm, G. V. M. Sharma, H. J. Hofmann, *Biopolymers* **2010**, *94*, 279.

[31] T. D. W. Claridge, J. M. Goodman, A. Moreno, D. Angus, S. F. Barker, C. Taillefumier, M. P. Watterson, G. W. J. Fleet, *Tetrahedron Lett.* **2001**, *42*, 4251.

[32] S. Hanessian, *Adv. Chem. Ser.* **1968**, *74*, 159.

[33] a) S. W. Johnson, S. F. Jenkinson (née Barker), D. Angus, I. Perez-Victoria, T. D. W. Claridge, G. W. J. Fleet, J. H. Jones, *J. Peptide Sci*. **2005**, *11*, 303; b) S. W. Johnson, S. F. Jenkinson (née Barker), J. H. Jones, D. J. Watkin, G. W. J. Fleet, *Tetrahedron: Asymm.* **2004**, *15*, 3263; c) D. J. Watkin, S. W. Johnson, J. H. Jones, G. W. J. Fleet, *Acta Cryst*. **2004** *E60*, o1609; d) S. W. Johnson, S. F. Jenkinson (née Barker), D. Angus, C. Taillefumier, J. H. Jones, G. W. J. Fleet, *Tetrahedron: Asymm.* **2004**, *15*, 2681.

[34] T. D. W. Claridge, B. Lopez-Ortega, S. F. Jenkinson, G. W. J. Fleet, *Tetrahedron: Asymm.* **2008**, *19*, 984.

[35] S. W. Johnson, G. W. J. Fleet, J. H. Jones, *J. Peptide Sci*. **2006**, *12*, 559.