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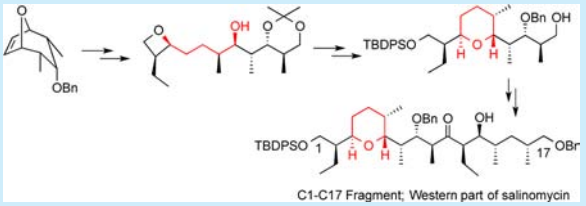
Formation of Substituted Tetrahydropyrans through Oxetane Ring Opening: Application to the Synthesis of C1−C17 Fragment of Salinomycin

J. S. Yadav,*[,†,‡] Vinay K. Singh,[†,‡] and P. Srihari[‡]

[†]Academy of Scientific and Innovative Research, [‡]Division of Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad-500007, India

Supporting Information

ABSTRACT: The stereoselective synthesis of C1−C17 fragment of salinomycin is achieved. The strategy employs a desymmetrization approach and utilizes an intramolecular oxetane opening reaction with *O*-nucleophile to result in the tetrahydropyran skeleton as the key step.



Polyketide natural products have played a crucial role in drug discovery as anticancer agents, antibiotics, and immune suppressants or antitubercular agents.[1] In 1974, Miyazaki[2a] et al., isolated a carboxylic polyether ionophore salinomycin **1** from the culture broth of *Streptomyces albus*. The X-ray crystallographic analysis of the *p*-iodophenacyl ester derivative[2b] of this molecule revealed the presence of a 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene motif which is rare in the polyether ionophores. Salinomycin is used commercially as an anti-coccidial for poultry (against gastrointestinal infection in birds and mammals) and as a growth promoter for the ruminants. Salinomycin is also used as an antibacterial[3] compound, and further investigations have shown that it can selectively kill breast cancer stem cells[4] and act as a P-gp inhibitor to overcome apoptosis resistance in human cancer cells, including leukemia stem cells.[5] The complex chemical structure and potent biological activity of salinomycin has attracted synthetic attention to pursue the total synthesis. First total synthesis of salinomycin was announced by Kishi et al.,[6] and was followed by several other syntheses as reported in the literature.[7] Herein, we have demonstrated a new protocol for the preparation of the substituted tetrahydropyran (THP) ring leading to the synthesis of a key fragment of salinomycin. The strategy may also find application in the synthesis of many other natural products such as narasin **2** and zincophorin **3**, having a similar structural motif (Figure 1).

Retrosynthetically, **1** (Scheme 1) was disconnected at the C17−C18 bond to reveal two key fragments as western fragment **4** (C1−C17) and an eastern fragment **5** (C18−C30). We initially focused on the synthesis of the western fragment (C1−C17) utilizing a substrate controlled *syn*-aldol reaction between benzylated *β*-hydroxy ketone **6** (segment A) and aldehyde **7** (segment B). The functionalized *trans*-THP **6** was envisioned to be constructed *via* an acid catalyzed intramolecular regioselective oxetane ring-opening reaction in exocyclization fashion followed by sequential functional group

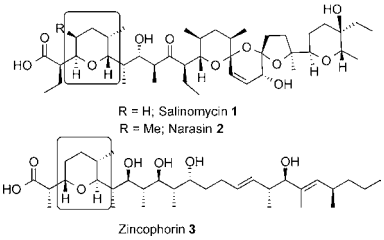


Figure 1. Substituted tetrahydropyran polyketides.

manipulations to extend the chain further. The oxetane ring in **8** would be synthesized by an Evans *syn*-aldol reaction of aldehyde **9** which in turn could be obtained from lactone **10**. **10** was easily accessed from acetal **11** in five steps. **11** was obtained from symmetric bicyclic olefin **12** following the well-known desymmetrization approach previously established by us.[8]

In continuation of our program on the total synthesis of polyketide natural products, we identified the symmetric precursor **12** for a desymmetrization strategy and have utilized it for the synthesis of several natural products.[8] Accordingly, compound **12** has been subjected to chiral hydroboration to yield **13** which was converted to known acetal[9] **11**. **11** on reduction with $LiAlH_4$ provided alcohol **14** in 93% yield (Scheme 2). **14** has all its stereochemical arrangement as present in natural salinomycin except for C2-methyl next to lactol functionality, which has to be epimerized. For this, the primary alcohol **14** was masked as the corresponding acetate **15** and treated with acetic acid, water, and THF (6:3:2) at 60 °C to yield lactol **16**. Oxidation of **16** with TEMPO-BAIB[10] afforded lactone **17** which was subjected to an epimerization reaction with a stoichiometric amount of DBU[11] to yield the desired lactone **10** in 92% yield. **10** was converted into

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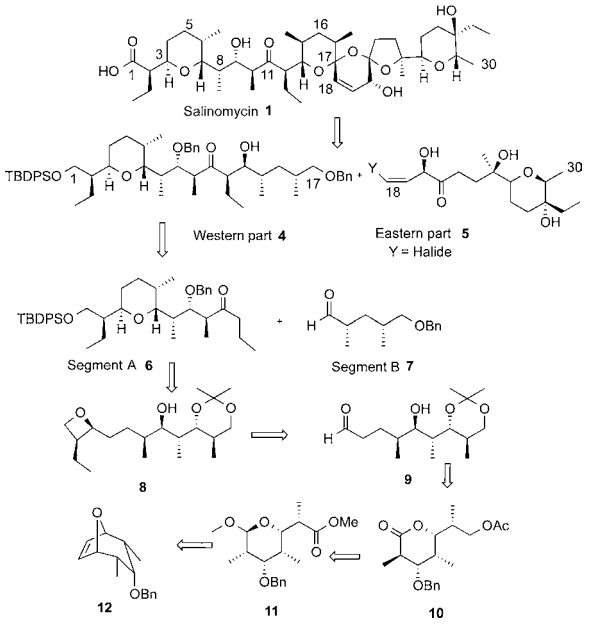
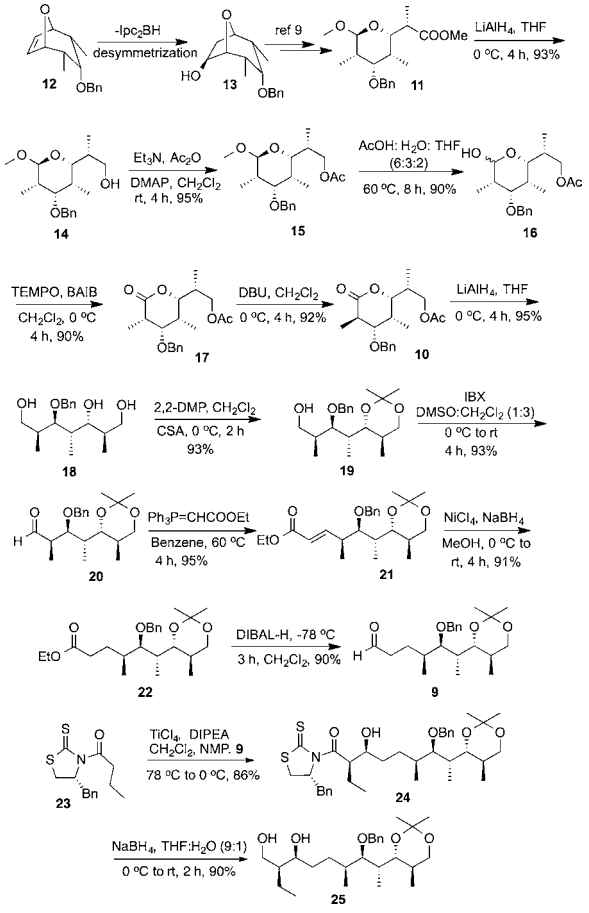
Scheme 1. Retrosynthesis



Scheme 2. Synthesis of Diol 25

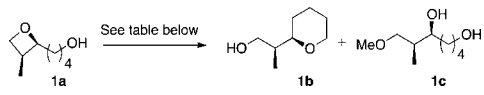


compound **19** through reduction with $LiAlH_4$ to yield **18** followed by treatment with 2,2-dimethoxypropane (2,2-DMP) in the presence of camphor sulfonic acid (CSA). Since it was required to extend the alkyl chain length we proceeded further with the oxidation of primary alcohol **19** with IBX[12] in DMSO to afford the aldehyde **20** which was subjected to the 2-carbon homologation reaction (2C-Wittig reaction) with $Ph_3P{=}CHCOOEt$ to afford α,β-unsaturated compound **21**. Conjugate reduction of the α,β-unsaturated compound with $NiCl_2{\cdot}6H_2O$ and $NaBH_4$[13] furnished saturated ester **22** which was further reduced by DIBAL-H at −78 °C to aldehyde **9** in 90% yield. Aldehyde **9** was subjected to the known aldol reaction based on the use of the thiazolidinethione chiral auxiliaries[14] reaction with thioimide **23**, to provide easily separable **24** in 86% yield. **24** was subjected to reductive cleavage with $NaBH_4$[15] to yield the diol **25**.

The diol **25** when subjected to Kishi's protocol[7a] for THP formation resulted in low yields,[16] which stimulated our search for an alternate procedure. Thus, we reasoned if the 1,3-diol is converted into the oxetane ring and subjected to a ring-opening reaction with an *O*-centered nucleophile in an intramolecular fashion may result in THP formation. Also, from the literature, though the oxetane ring opening by a carbon nucleophile is well-known[17] the same is least known with heteroatom nucleophiles.[18] As per the literature precedence, only one report from Jacobsen et al., wherein an example pertaining to THP skeleton formation[19] was observed during the enantioselective intramolecular opening of oxetanes for obtaining enantioenriched tetrahydrofurans. The scope and generality for this reaction has not yet been explored further as a synthetic protocol for the THP formation. Thus, in the present context, we report our studies for the intramolecular oxetane ring-opening reaction with an *O*-centered nucleophile to result in a substituted THP moiety.

To begin, we examined the compound **1a** by exposing it to acids in the presence of protic and aprotic solvents (Scheme 3).

Scheme 3. Optimization for the Intramolecular Oxetane Ring-Opening Reaction with Simultaneous THP Ring Formation



Although the exocyclic oxetane ring opening occurred in the presence of ±CSA, *p*TSA, PPTS, and other Lewis acids such as $BF_3{\cdot}OEt_2$, $SnCl_4$, and $TiCl_4$ in the presence of CH_2Cl_2, when methanol was used as the solvent/cosolvent, the corresponding methyl ether rather than the THP ring was formed (Table 1, entries 1−3). This may be attributed toward the more nucleophilic nature of methanol. The reaction also worked with *i*-PrOH; yet, it proceeded for longer durations with low

Table 1. Optimization of THP Ring Formation Reaction

entry	reaction conditions acid\solvent\temperature\time	product ratio in % yield **1b/1c**
1	*p*TSA or CSA or PPTS, MeOH, 0 °C to rt, 1 h	0/93
2	PPTS, MeOH, 0 °C to rt, 3 h	5/85
3	*p*TSA, MeOH: CH_2Cl_2 (1:1), 0 °C to rt, 1 h	5/85
4	CSA, *i*-PrOH, 0 °C to rt, 36 h	10/0[a]
5	CSA, CH_2Cl_2, 0 °C to rt, 4 h	95/0
6	$BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to rt, 18 h	70/0
7	$TiCl_4$, CH_2Cl_2, 0 °C to rt, 28 h	89/0
8	$SnCl_4$, CH_2Cl_2, 0 °C to rt, 24 h	88/0
9	CSA, or *p*TSA, CH_2Cl_2:*i*-PrOH, (15:1), 0 °C to rt, 2-2.5 h	94/0

[a]85% of starting material was recovered.

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yields. When an aprotic solvent such as CH_2Cl_2 was used, the reaction proceeded smoothly for the desired conversion. Interestingly, the duration of the reaction was reduced when the mixture CH_2Cl_2/*i*-PrOH (15:1) was utilized (entry 9, Table 1). Encouraged by these results, additional substrates with varying levels of complexity were used to test the scope of the presently developed methodology (Table 2, entries 2−10). Gratifyingly, all the substrates underwent a clean oxetane ring-opening reaction in an exocyclic fashion yielding the corresponding substituted THP ring.

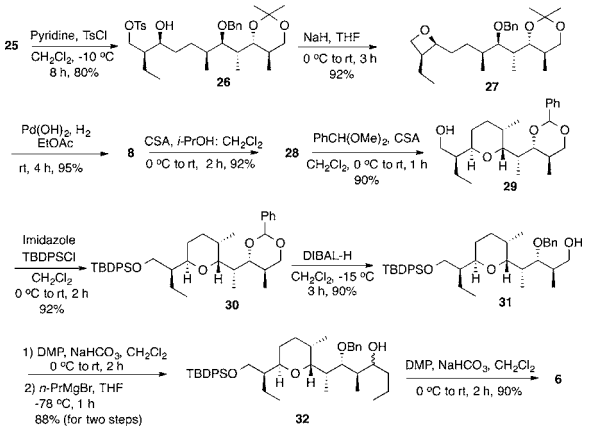
Table 2. Examples for Intramolecular Oxetane Ring-Opening Reactions Leading to THP Skeleton

entry	substrate	product[a]	time (in h)	yield (%)[b]
1	**1a**	**1b**	2	94
2	**2a**	**2b**	2	94
3	**3a**	**3b**	2	93
4	**4a**	**4b**	2	92
5	**5a**	**5b**	2	93
6	**6a**	**6b**	2	91
7	**7a**	**7b**	48	70
8	**8a**	**8b**	2	80
9	**9a**	**9b**	2	80
10	**8**	**28**	2	92

[a]The products were obtained after treating the substrate with CSA in the presence of iPrOH at 0 °C. [b]The yields obtained are isolated yields, and the products obtained were characterized by ^{1}H NMR.

With the positive results and optimized reaction conditions, we proceeded further. Selective monotosylation of the primary hydroxyl group in **25** afforded **26** which on exposure to NaH gave oxetane **27**. Palladium hydroxide mediated debenzylation of **27** afforded secondary alcohol **8** to serve as the main precursor for the THP ring formation reaction. Thus, **8** upon exposure to ±CSA underwent a smooth ring-opening and -closing reaction to yield the triol **28** (Table 2, entry 10, and Scheme 4). The stereochemical arrangement and absolute configuration were confirmed after proceeding further by masking the 1,3-diol functionality in **28** as the corresponding benzaldehyde acetal **29** by X-ray crystallography (see Supporting Information (SI)).[20] The free hydroxyl group in **29** was protected as the corresponding silyl ether derivative **30** with TBDPSCl and imidazole and then subjected to regioselective reductive acetal cleavage at the less hindered oxygen with DIBAL-H[21] to afford the primary alcohol **31**. **31** was oxidized using Dess-Martin periodinane[22] and was treated

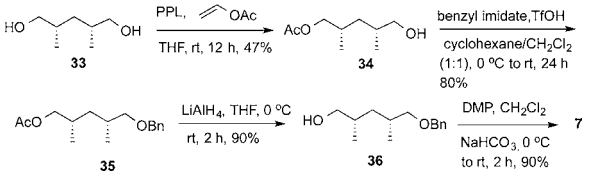
Scheme 4. Synthesis of Segment A 6



with *n*-propylmagnesium bromide to furnish alcohol **32** as a diastereomeric mixture in 88% yield over two steps. The mixture of secondary alcohols **32** without further separation was oxidized using Dess-Martin periodinane to obtain ketone **6** (segment A, C1−C13 fragment).

Our approach for the synthesis of aldehyde **7** (segment B C13−C17) is delineated in Scheme 5. Accordingly, the

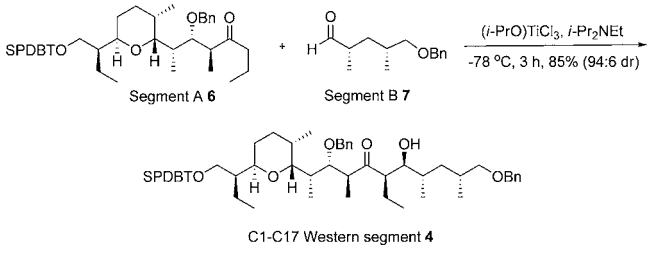
Scheme 5. Synthesis of Segment B 7



synthesis began with the known diacid[23] which on reduction with $LiAlH_4$ provides precursor *meso* diol **33** that was subjected to desymmetrization by using porcine pancreatic lipase (PPL) and vinyl acetate in THF at ambient conditions furnishing the monoacetate **34** in 47% yield with ≥95% *ee* along with the *meso*-diacetate.[24] Alcohol **34** was converted into corresponding benzyl ether **35** and subjected to reduction with $LiAlH_4$ to yield alcohol **36**. Oxidation of **36** with Dess-Martin periodinane provided segment B **7** in 90% yield.

After the successful synthesis of segments A **6** and B **7**, we proceeded further to assemble them together toward the synthesis of the C1−C17 fragment as shown in the Scheme 6. The reaction was performed under substrate controlled aldol reaction following Urpi's[25] procedure wherein the reaction occurs *via* the *Z*-enolate of ketone **6** that adds on to aldehyde **7** through a chelating chairlike transition state resulting in the

Scheme 6. Coupling of Segment A and B



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formation of product with a *syn* configuration at the newly generated stereocenters.

In conclusion, we have demonstrated an intramolecular regioselective oxetane ring-opening reaction to install the THP ring which can be useful for the synthesis of natural products having pyran motifs. Once again the desymmetrization strategy proved to be pivotal for the western part **4** (C1−C17 segment) synthesis of salinomycin. The synthesis involved 24 steps starting from ester **11** with a 10.2% overall yield. Further work toward the total synthesis of salinomycin is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yadavpub@iict.res.in.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Williams, P. G.; Asolkar, R. N.; Kondratyuk, T.; Pezzuto, J. M.; Jensen, P. R.; Fenical, W. *J. Nat. Prod.* **2007**, *70*, 83.

(2) (a) Miyazaki, Y.; Shibuya, M.; Sugawara, H.; Kawaguchi, O.; Hirose, C.; Nagatsu, J.; Esumi, S. *J. Antibiot.* **1974**, *27*, 814. (b) Kinashi, H.; Otake, N.; Yonehara, H.; Sato, S.; Saito, Y. *Tetrahedron Lett.* **1973**, *49*, 4955.

(3) (a) Ruff, M. D. Veterinary Applications. In *Polyether Antibiotics*; Westley, J. W., Ed.; Marcel Dekker, Inc.: New York and Basel, 1982. (b) Dutton, C. J.; Banks, B. J.; Cooper, C. B. *Nat. Prod. Rep.* **1995**, *12*, 165. (c) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407.

(4) Gupta, P. B.; Onder, T. T.; Jiang, G.; Tao, K.; Kuperwasser, C.; Weinberg, R. A.; Lander, E. S. *Cell* **2009**, *138*, 645.

(5) Kim, J. H.; Chae, M. J.; Kim, W. K.; Kim, Y. J.; Kang, H. S.; Kim, H. S.; Yoon, S. Br. *J. Pharmacol.* **2011**, *162*, 773.

(6) Kishi, Y.; Hatakeyama, S.; Lewis, M. D. Total Synthesis of Narasin and Salinomycin. In *Frontiers of Chemistry*; Laidler, K. J., Ed.; Pergamon Press: Oxford, 1982.

(7) (a) Tino, J. A.; Lewis, M. D.; Kishi, Y. *Heterocycles* **1987**, *25*, 97. (b) Horita, K.; Oikawa, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1698. (c) Horita, K.; Nagato, S.; Oikawa, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1705. (d) Horita, K.; Oikawa, Y.; Nagato, S.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1717. (e) Horita, K.; Nagato, S.; Oikawa, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1726. (f) Kocienski, P. J.; Brown, R. C. D.; Pommier, A.; Procter, M.; Schmidt, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 9. (g) Larossa, I.; Romea, P.; Urpi, F. *Org. Lett.* **2006**, *8*, 527. (h) Brazeau, J. F.; Guilbaut, A.-A.; Kochuparampil, J.; Mochirian, P.; Guindon, Y. *Org. Lett.* **2010**, *12*, 36.

(8) (a) Yadav, J. S.; Rao, S. C.; Chandrasekhar, S.; Rama Rao, A. V. *Tetrahedron Lett.* **1995**, *36*, 7717. (b) Yadav, J. S.; Abraham, S.; Reddy, M. M.; Sabitha, G.; Ravi Sanker, A.; Kunwar, A. C. *Tetrahedron Lett.* **2001**, *42*, 4713. (c) Yadav, J. S.; Ahmed, M. M. *Tetrahedron Lett.* **2002**, *43*, 7147. (d) Yadav, J. S.; Srinivas, R.; Sathaiah, K. *Tetrahedron Lett.* **2006**, *47*, 1603. (e) Yadav, J. S.; Pratap, T. V.; Rajender, V. *J. Org. Chem.* **2007**, *72*, 5882. (f) Yadav, J. S.; Rajender, V.; Gangadhara Rao, Y. *Org. Lett.* **2010**, *12*, 348. (g) Yadav, J. S.; Dhara, S.; Hossain, S. S.; Mohapatra, D. K. *J. Org. Chem.* **2012**, *77*, 9628.

(9) (a) Yadav, J. S.; Hossain, S. S.; Madhu, M.; Mohapatra, D. K. *J. Org. Chem.* **2009**, *74*, 8822. (b) Yadav, J. S.; Hossain, S. S.; Mohapatra, D. K. *Tetrahedron Lett.* **2010**, *51*, 4179.

(10) Hansen, M. T.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, N. J.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57.

(11) Yadav, J. S.; Abraham, S.; Reddy, M. M.; Sabitha, G.; Ravi Sanker, A.; Kunwar, A. C. *Tetrahedron Lett.* **2001**, *42*, 4713.

(12) Frigeno, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.

(13) Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 817.

(14) (a) Crimmins, M. T.; Dechert, A. M. R. *Org. Lett.* **2012**, *14*, 2366. (b) Crimmins, M. T.; Slade, D. J. *Org. Lett.* **2006**, *8*, 2191. (c) Crimmins, M. T.; Dechert, A. M. R. *Org. Lett.* **2009**, *11*, 1635. (d) Crimmins, M. T.; She, J. *Synlett* **2004**, 1371.

(15) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.

(16) The primary alcohol of diol **25** was selectively protected as corresponding TBDPS-ether, and the secondary alcohol was mesylated and then subjected to debenzylation to give the precursor for THP formation. Our attempts for cyclization following Kishi's procedure resulted in the desired THP ring with a 40% yield.

(17) (a) Paterson, I.; Delgado, O. *Tetrahedron Lett.* **2003**, *44*, 8877. (b) Trost, B. M.; Wrobleski, S. T.; Chisholm, J. D.; Harrington, P. E.; Jung, M. *J. Am. Chem. Soc.* **2005**, *127*, 13589. (c) Bunte, J. O.; Cuzzupe, A. N.; Daly, A. M.; Rizzacasa, M. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6376. (d) Yadav, J. S.; Basak, A. K.; Srihari, P. *Tetrahedron Lett.* **2007**, *48*, 2841. (e) Gersbach, P.; Jantsch, A.; Feyen, F.; Scherr, N.; Dangy, J. P.; Pluschke, G.; Altmann, K. H. *Chem.—Eur. J.* **2011**, *17*, 13017.

(18) For the oxetane ring opening reaction with heteroatoms as nucleophiles, see: (a) Dussault, P. H.; Dai, P. *Org. Lett.* **2002**, *4*, 4591. (b) Wirsching, J.; Schulze, O.; Voss, J.; Giesler, A.; Kopf, J.; Adiwidjaja, G.; Balzarini, J.; Clerq, E. D. *Nucleosides, Nucleotides and Nucleic Acids* **2002**, *21*, 257. (c) Whistler, R. L.; Luttenegger, T. J; Rowell, R. M. *J. Org. Chem.* **1968**, *33*, 396. (d) Pavle, H.; Nada, V.; Mirjana, P.; Janos, C. *J. Serb. Chem. Soc.* **2001**, *66*, 1. (e) Rondestvedt, C. S., Jr. *J. Org. Chem.* **1961**, *26*, 3024. (f) Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 1190. (g) Chini, M. *Tetrahedron Lett.* **1994**, *35*, 761.

(19) (a) Loy, R. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 2786. For other methods, see: (b) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045.

(20) See SI for details of X-ray crystallography CCDC No. 934894.

(21) Schreiber, S. L.; Wang, Z.; Schulte, G. *Tetrahedron Lett.* **1988**, *29*, 4085.

(22) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(23) Prepared in two steps: (a) Miller, J. J.; De Benneville, P. L. *J. Org. Chem.* **1957**, *22*, 1268. (b) Stork, G.; Nair, V. *J. Am. Chem. Soc.* **1979**, *101*, 1315. (c) Wolfrom, M. L.; Bobbitt, J. M. *J. Am. Chem. Soc.* **1956**, *78*, 2489.

(24) (a) Tsuji, K.; Terao, Y.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 6189. (b) Lin, G.; Xu, W. *Tetrahedron* **1996**, *52*, 5907. (c) Anderson, J. C.; Ley, S. V.; Marsden, S. P. *Tetrahedron Lett.* **1994**, *35*, 2087. (d) Fujita, K.; Mori, K. *Eur. J. Org. Chem.* **2001**, 493. (e) McAllister, G. D.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 2551. (f) Yadav, J. S.; Yadav, N. N.; Rao, T. S.; Reddy, B. V. S.; Al-Ghamdi, A. A. K. *Eur. J. Org. Chem.* **2011**, 4603.

(25) Solsona, G. J.; Nebot, J.; Romea, P.; Urpi, F. *J. Org. Chem.* **2005**, *70*, 6533.