ORGANIC LETTERS

2005
Vol. 7, No. 16
3569−3572

A Scalable Route to Trisubstituted (*E*)-Vinyl Bromides

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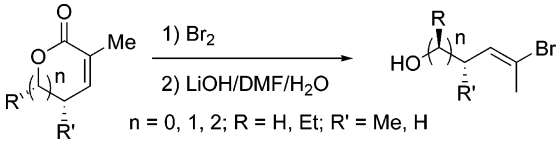
Received June 13, 2005

ABSTRACT

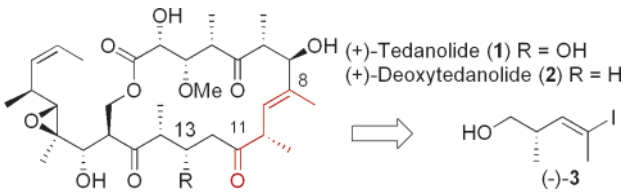


An effective, readily scalable two-step synthesis of trisubstituted (*E*)-vinyl bromides involving bromination of α,β-unsaturated lactones followed by hydrolytic fragmentation has been developed. Several trisubstituted (*E*)-vinyl bromides, including multigram quantities of (+)-(*E*)-4-bromo-2-methyl-3-pentenol, a synthetic intermediate required for the C(8)–C(11) moieties of (+)-tedanolide (1) and (+)-13-deoxytedanolide (2), illustrate the utility of this protocol.

Trisubstituted (*E*)-halo alkenes comprise important synthetic intermediates often employed in natural product total syntheses, in particular for macrolides such as scyphostatin,[1] octalactin,[2] phomactin,[3] borrelidin,[4] apoptolidin,[5] FK901464,[6] phorboxazole A,[7] fostriecin,[8] taxifolial A,[9] and kendomycin,[10] tedanolide (**1**), and deoxytedanolide (**2**).[11]

In connection with our continuing interest in defining the biochemical mode of action of architectually complex macrolides, we recently initiated preparative-scale syntheses of both (+)-tedanolide (**1**) and (+)-13-deoxytedanolide (**2**), based on our now successful first-generation synthesis of 13-deoxytedanolide (**2**). For this venture we required multigram quantities of (*E*)-vinyl iodide **3** to serve as the C(8)−C(11) fragment (Scheme 1). Although our first generation

Scheme 1



route to (−)-**5**, employing the Pd-catalyzed hydrostannylation of alkyne (−)-**4** followed by iodination, proved effective, a somewhat difficult to separate mixture (ca. 6:1) of the *E*- and *Z*-isomers resulted (eq 1, Scheme 2).

We reasoned that hydrozirconation might be more effective given the anticipated efficiency and higher *E*-selectivity after the iodination (eq 2).[1−6] This reaction sequence, however,

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(1) Inoue, M.; Yokota, W.; Murugeshi, M. G.; Izuhara, T.; Katoh, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 4207.
(2) O'Sullivan, P. T.; Buhr, W.; Fuhry, M. A. M.; Harrison, J. R.; Davies, J. E.; Feeder, N.; Marshall, D. R.; Burton, J. W.; Holmes, A. B. *J. Am. Chem. Soc.* **2004**, *126*, 2194.
(3) Mohr, P. T.; Halcomb, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 1712.
(4) Duffey, M. O.; LeTiran, A.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 1458.
(5) Nicholaou, K. C.; Li, Y.; Sugita, K.; Monenschein, H.; Guntupali, P.; Mitchell, H. J.; Fylaktakidou, K. C.; Vourloumis, D.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2003**, *125*, 15443.
(6) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974.
(7) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M.; *J. Am. Chem. Soc.* **2001**, *123*, 4834.
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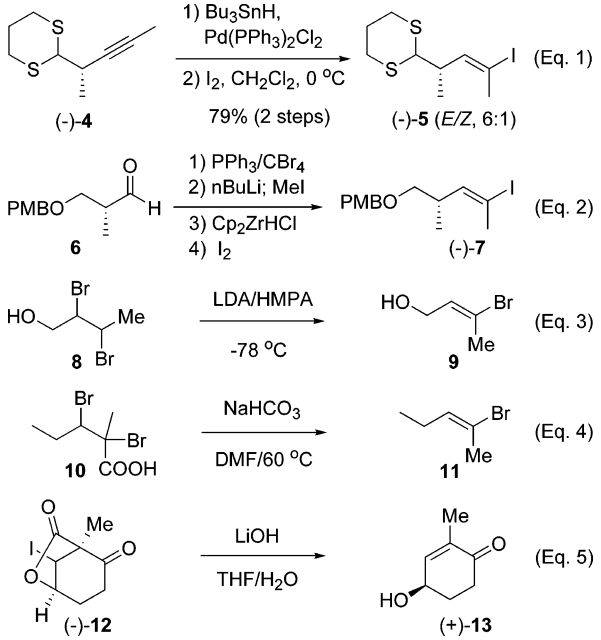
(9) Commeiras, L.; Santelli, M.; Parrain, J.-L. *Org. Lett.* **2001**, *3*, 1713.
(10) Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720.
(11) (a) Smith, A. B., III; Adams, C. M.; Lodise-Barbosa, S. A.; Degnan, A. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12042. (b) Smith, A. B., III; Adams, C. M.; Lodise-Barbosa, S. A.; Degnan, A. P. *J. Am. Chem. Soc.* **2003**, *125*, 350. (c) Smith, A. B., III; Lodise-Barbosa, S. A. *Org. Lett.* **1999**, *1*, 1249.

10.1021/ol051376q CCC: $30.25
Published on Web 07/15/2005

Scheme 2

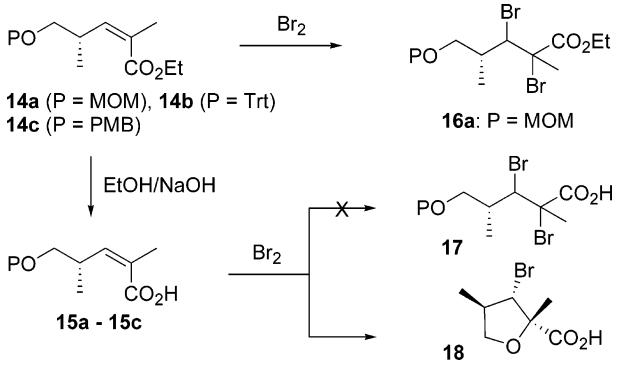


requires the use of excess Schwartz reagent, rendering large-scale application both expensive and possibly cumbersome. Additional concerns include the large-scale use of PPh_3 and CBr_4 in the Corey−Fuchs protocol[12] en route to the requisite 2-alkyne. Alternative methods based on stannocupration[7−10,13] and/or silanocupration[14] would also require 3−5 equiv of expensive reagents and as such did not appear attractive for large-scale synthesis.

A careful survey of the literature revealed few alternatives. Roush and co-workers, in their elegant work directed at the total syntheses of kijanolide and tetronolide,[15] prepared (*E*)-3-bromo-2-butenol **9** from erythro-2,3-dibromobutanol **8** in 50% yield, upon treatment with LDA (eq 3). Their approach, however, was not immediately applicable to our system, given the regioselectivity issue upon HBr elimination. An innovative two-step sequence to (*E*)-vinyl bromide **11** was reported by Cha et al. (eq 4).[16] A similar fragmentation was observed by Khim and co-workers to furnish **13** as a byproduct from iodolactone **12** (eq 5).[17]

Direct application of the Cha sequence in our system, however, did not prove straightforward because of the incompatibility of various hydroxyl protecting groups during the bromination step, in conjuction with the required hydrolysis of unsaturated ester **14** to acid **15** for the fragmentation protocol (Scheme 3).

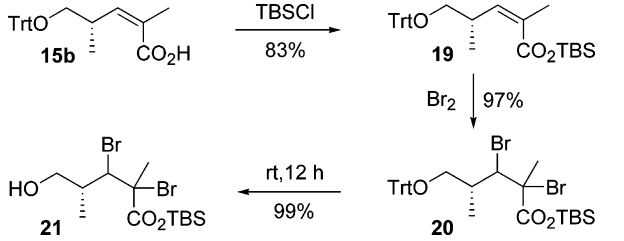
Scheme 3. Bromination of Enoic Acid and Enoate



For example, with **15a** or **15b** bearing an acid-labile group, bromination not surprisingly produced tetrahydrofuran **18** instead of dibromide **17**. Apparently, trace HBr generated during the bromination unmasked the protected hydroxyl, which in turn intercepted the bromonium intermediate to provide bromoether **18**. Attempts to remove trace acid from the reaction mixture by adding $NaHCO_3$, Na_2CO_3, or Et_3N did not improve the reaction; only complex product mixtures resulted. In case of **15c** bearing a PMB group, aromatic bromination occurred before that of the olefin. Alternatively, bromination of ethyl ester **14a** cleanly afforded dibromide **16a**. However, subsequent hydrolysis of **16a** resulted in concomitant β-elimination of HBr. A similar result was obtained with the methyl ester.

Ester **19** possessing the more readily removable TBS group was prepared next from **15b** (Scheme 4). Although bromination furnished the dibromide **20** in excellent yield (ca. 97%), **20** proved too unstable to be easily manipulated. For example, pure **20** loses the trityl group to provide alcohol **21** upon standing overnight at room temperature.

Scheme 4

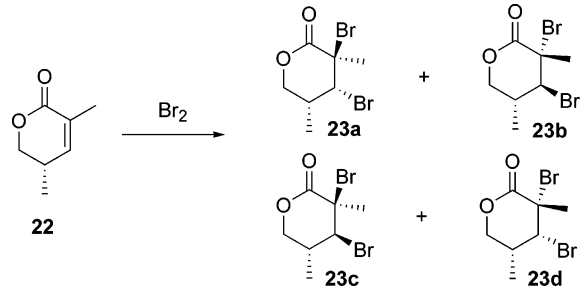


Taken together, these results suggest the use of an α,β-unsaturated lactone, comprising internal protection of the hydroxyl group and at the same time imposing at most modest steric hindrance for the hydrolysis step compared with the acyclic counterpart.

We first focused on unsaturated lactone **22**.[18] Surprisingly, bromination furnished all four possible diastereomers, two

(12) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(13) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768.
(14) (a) Archibald, S. C.; Barden, D. J.; Bazin, J. F. Y.; Fleming, I.; Foster, C. F.; Mandal, A. K.; Mandal, A. K.; Parker, D.; Takaki, K.; Ware, A. C.; Williams, A. R. B.; Zwicky, A. B. *Org. Biomol. Chem.* **2004**, *2*, 1051. (b) Fleming, I.; Newton, T. W.; Roessler, *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527.
(15) Roush, W. R.; Brown, B. B. *J. Am. Chem. Soc.* **1993**, *115*, 2268.
(16) (a) Jeffery, D. W.; Perkins, M. V.; White, J. M. *Org. Lett.* **2005**, *7*, 1581. (b) Kim, H.; Lee, S.-K.; Lee, D.; Cha, J. K. *Synth. Commun.* **1998**, *28*, 729. (c) Overman, L. E.; Shim, J. *J. Org. Chem.* **1993**, *58*, 4662.
(17) Khim, S.-K.; Dai, M.; Zhang, X.; Chen, L.; Pettus, L.; Thakkar, K.; Schultz, A. G. *J. Org. Chem.* **2004**, *69*, 7728.

Scheme 5. Bromination of Lactone (+)-**22**



trans- (**23a** and **23b**) and two *cis*-isomers (**23c** and **23d**) as depicted in Scheme 5. The ratio determined by ^{1}H NNR was 50:25:5:1, respectively. The relative stereochemistries of **23a**−**c**, initially assigned via ^{1}H NMR coupling constants of the adjacent methine protons, were in each case confirmed by X-ray crystallography. Presumably formation of the *cis*-dibromides (**23c** and **23d**) arises via the intermediacy of the C(3) carbocation rather than the conventional bromonium ion, with possible stabilization by the lactone ether oxygen atom.[19]

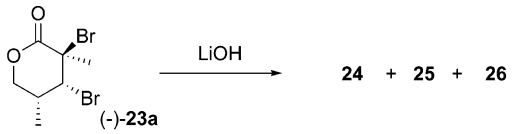
The *cis*-dibromide was, of course, a significant issue, as only the *trans*-isomers were expected to furnish the desired trisubstituted (*E*)-vinyl bromide upon hydrolysis and subsequent fragmentation.[16b] Fortunately separation of the dibromide isomers, and in particular removal of the *cis*-bromides, proved readily achievable by flash chromatography.

Best selectivity in the bromination was obtained when the reaction was conducted in CH_2Cl_2 with 3 equiv of Br_2 over a temperature range of −10 to 0 °C (cf. total isolated yield, 78%; *trans*/*cis* ratio > 10:1). Methylene chloride furnished slighly higher yields than than CCl_4, $CHCl_3$, or ether. Reaction temperatures higher than 0 °C increased formation of the undesired *cis*-isomers, whereas temperatures below −10 °C provided no advantage in terms of yield or the *trans*/*cis* ratio. The minor *trans*-dibromide **23b** proved quite unstable upon silica gel column chromatography.

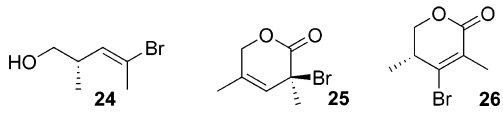
The hydrolytic fragmentations proceeded under somewhat different conditions for **23a** and **23b**. For example, treatment of **23b** with lithium hydroxide in DMF readily led to (*E*)-vinyl bromide **24** in near quantitative yield, whereas similar treatment of **23a**, possessing the C(3)Br and C(4)H oriented anti-coplanar, required significant optimization, as not only the desired vinyl bromide **24** but also elimination products **25** and **26** resulted, depending on the exact reaction conditions employed (cf. Table 1).

Best results for the hydrolytic fragmentation involved DMF/H_2O as a 4:1 mixture (entry 6). Under these conditions, the desired trisubstituted (*E*)-vinyl bromide **24** (>99:1 *E* to *Z* by NMR) was obtained in 73% yield from **23a**. Without H_2O, the reaction gave predominantly elimination product

Table 1. Tandem Hydrolysis−Fragmentation of (−)-**23a**



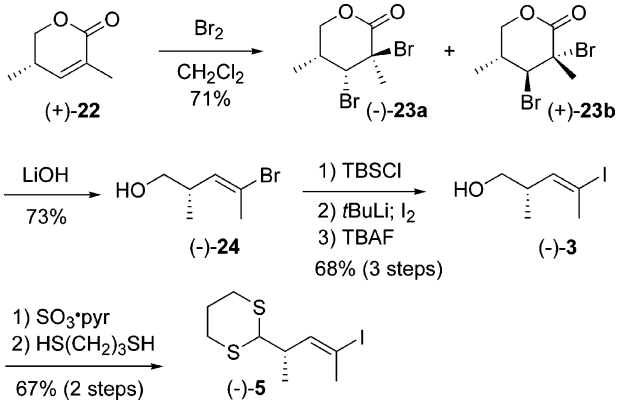
entry	equiv	conditions	result (isolated yield)
1	3.0	DMF/rt/12 h	**24** (37%), **25** (40%), **26** (7%)
2	3.0	DMF/70 °C/2 h	**24** (trace), **25** (62%)
3	1.5	THF/H_2O (9:1)/12 h	**24** (30%), **25** (27%)
4	5.0	MeCN/rt/12 h	low conversion
5	2.0	DMF/H_2O (9:1)/rt/16 h	**24** (65%)
6	3.0	DMF/H_2O (4:1)/rt/12 h	**24** (71%)



25. With additional H_2O, the reaction did not go to completion, thereby diminishing the yield. Elevation of the reaction temperature resulted in the increased formation of the elimination products **25** and **26**. For the base, lithium hydroxide proved uniformly superior to NaOH or $Ba(OH)_2$ in terms of yield. Direct subjection of the bromination mixture to the hydrolytic fragmentation conditions, without chromatographic removal of the *cis*-dibromides, improved the overall yield (52% → 67% from **22**), albeit with modest sacrifice of the stereochemical purity of **24** (ca. *E*/*Z*, 10:1).

To demonstrate the scalability of the two-step bromination-hydrolytic fragmentation sequence, multigram quantities (ca. 13 g) of bromide **24** were prepared from (+)-**22** (Scheme 6).[20] Both relative and absolute stereochemical integrity of

Scheme 6. Preparation of (+)-**23**



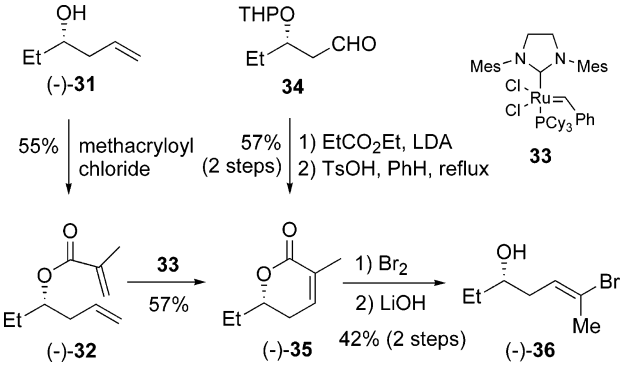
(−)-**24** were confirmed by conversion to (*E*)-vinyl iodide **5**.[21]

(18) (a) Yoneda, E.; Zhang, S.-W.; Zhou, D.-Y.; Onitsuka, K.; Takahashi, S. *J. Org. Chem.* **2003**, *68*, 8571. (b) Andrus, M. B.; Li, W.; Keyes, R. F. *J. Org. Chem.* **1997**, *62*, 5542. (c) Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118.

(19) Bromination of 2-methyl-2-cyclohexenone provided a single dibromide (e.g., *trans*-2,3-dibromo-2-methyl cyclohexanone).

(20) The vinyl iodide (−)-**3** can be prepared from (*R*)-(−)-Roche's ester via the route in eq 2 in eight steps with 30% overall yield. Also see: Organ, M. G.; Wang, J. *J. Org. Chem.* **2003**, *68*, 5568.

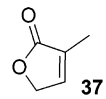
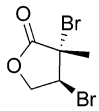
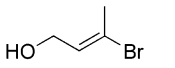
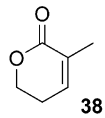
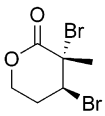
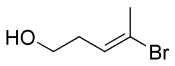
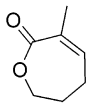
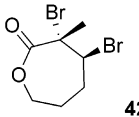
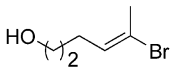
Scheme 7. Preparation of (−)-**36**



Application of the two-step bromination decarboxylation-debromination sequence to lactone (−)-**35** (Scheme 7), readily available either by ring-closing metathesis (RCM) from **32** or by aldol reaction of **34** followed by lactonization, furnished bromide (−)-**36**, a key subunit in our on going program to construct the potent cytotoxic agent, irciniastatin A.[22] Importantly, this sequence could be carried out on a gram scale.

In similar fashion, commercially available 3-methyl butenolide **37** provided 2-bromo-2-butenol **43** in 55% overall yield (Table 2). For **38** and **39**,[23] formation of the undesired *cis*-dibromides became a more significant problem, reducing the yields of the *trans*-dibromide **41** and **42**. Separation of the *cis*-bromides from the *trans*-isomers again proved straightforward. Subsequent hydrolytic fragmentation afforded vinyl bromides **44** and **45**[24] in 80% and 62% isolation yield, respectively.

Table 2.

lactone	*trans*-dibromide	(*E*)-vinyl bromide
 **37**	 **40** (93%)	 **43** (59%)
 **38**	 **41** (65%)	 **44** (80%)
 **39**	 **42** (55%)	 **45** (62%)

Acknowledgment. Financial support was provided by the National Instituted of Health (Institute of General Medical Science) through grant GM 29028. C.-G.C. is grateful for financial support from Hanyang University (HY-2004-I).

Supporting Information Available: Details of experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051376Q

(21) Smith, A. B., III; Gallagher, W. P. Unpublished results.

(22) Pettit, G. R.; Xu, J.-P.; Chapuis, J.-C.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schmidt, J. M. *J. Med. Chem.* **2004**, *47*, 1149.

(23) Prepared from δ-valerolactone (55%, 2 steps); see: Slouggi, N.; Rousseau, G. *Tetrahedron* **1985**, *41*, 2643. Both **38** and **39** are also available via the RCM or aldol route used for (−)-**35** in Scheme 7.

(24) Marumoto, S.; Kogen, H.; Naruto, S. *Tetrahedron* **1999**, *55*, 7145.