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Novel iodine catalyzed diastereoselective synthesis of *trans*-2,6-disubstituted tetrahydro-2*H*-pyrans: synthesis of C1–C13 fragment of bistramide-A

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ABSTRACT

A new method for the stereoselective synthesis of *trans* 2.6-disubstituted tetrahydro-2*H*-pyrans has been developed involving iodine catalyzed allylation of tetrahydro-2*H*-pyranol with excellent *trans* selectivity. The method was also applied toward the construction of C1–C13 fragment of bistramide-A in 11 steps with 21.4% overall yield.

Tetrahydropyrans (THP) containing natural products are widely present in nature and show pronounced biological activities.[1] In particular, 2,6-disubstituted tetrahydro-2*H*-pyran ring moieties are found in several of them, namely Phorboxazole A&B,[2] Leucascandrolide A,[3] Apicularen A,[4] Aspergillide B,[5] etc., having significant properties and importance (Fig. 1). As a result, construction of the THP ring is always in demand and till date several approaches[6] have been reported that involves activation of glycals with different Lewis acid,[7] Petasis–Ferrier rearrangement,[8] Hetero Diels–Alder cycloaddition,[9] epoxide opening,[10] oxa-conjugate addition,[11] Prins reaction,[12] tandem cross metathesis/iodocyclization,[13] intramolecular silyl modified Sakurai reaction,[14] and Maitland–Japp reaction.[15]

We began our investigation after attention was drawn on one of our earlier reports, where formation of 2,6-disubstituted-3,4-dihydropyrans was demonstrated from δ-hydroxy α,β-unsaturated aldehydes catalyzed by molecular iodine.[16] The existence of the double bond in these moieties was found to be of limitation toward the synthesis of certain natural products with saturated DHP core, wherein reduction reactions are unavoidable in the later stage. To support the fact, herein, we prepared such a particular skeleton of substituted tetrahydro-2*H*-pyranol and subjected it to C-allylation conditions (Scheme 1).

Initially, we investigated compound **3** which upon iodine catalyzed cyclization furnished C-allylated tetrahydro-2*H*-pyran **13** in 88% yields. To our notice, ^{1}H NMR and ^{13}C NMR spectrum revealed formation of only one isomer. Further investigation under chiral HPLC showed a slight existence of other diastereomers in 9:1 ratio, better compared to the earlier report of 7:3 ratio.[17] The NOE investigation supported the 2,6-*trans* relationship in the desired compound (Fig. 2). Further the investigation was extended to different tetrahydro-2*H*-pyrans for wider applicability and afforded the corresponding C-allylated product in better yields and ratio (Table 1).

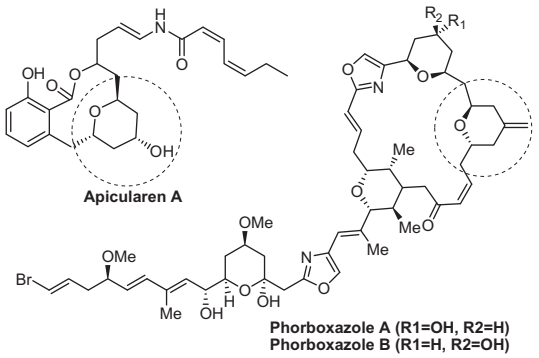

Figure 1. Selective examples of THP containing natural products.

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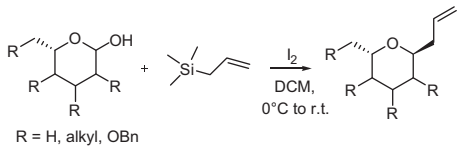


Scheme 1. General reaction of C-allylation of tetrahydro-2*H*-pyranol.

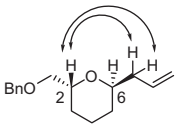
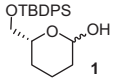
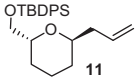
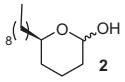
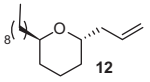
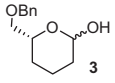
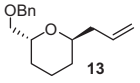
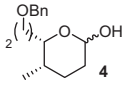
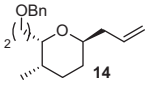
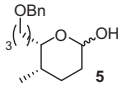
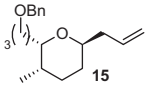
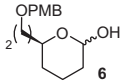
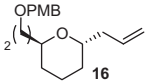
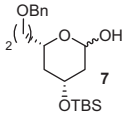
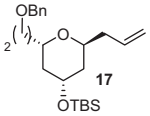
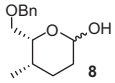
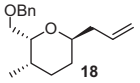
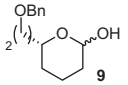
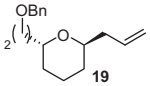
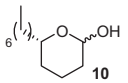
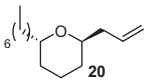


Figure 2. Characteristic NOE of compound **13**.

Table 1
Iodine-catalyzed stereoselective synthesis of *trans*-2,6-disubstituted-2*H*-pyrans[31]

Entry	Substrate	Product[a]	Time (h)	Yield[b] (%)	Ratio[c] (*de*)
1			0.5	88	99:1
2			0.5	85	—
3			0.5	88	9:1
4			0.5	85	9:1
5			0.25	85	9:1
6			1.0	90	9:1
7			1.0	86	9:1
8			0.5	88	99:1
9			0.5	91	99:1
10			0.5	87	—

[a] The products were characterized by ^{1}H NMR, IR, and mass spectrometry.
[b] Yield refers to pure products after chromatography.
[c] Determined by HPLC analysis on a mobile phase discovery C8 250 × 4.6 mm, 5μ column.

The possible reaction mechanism may involve activation of oxocarbenium ion by the trimethyl silyl group followed by attack of allyl group from *anti* direction with respect to sixth position bearing group favored by stereoelectronic factors.[16]

After this encouraging result, we focused toward its application for the synthesis of a C1–C13 tetrahydropyran core unit of bistramide-A, (Fig. 3) which is a marine metabolite isolated from *Lissoclinum Bistratum* in 1988 by Verbist and co-workers.[18a] Bistramide B, C, D, and K were reported by 1994[18b] and these classes of compounds showed significant cytotoxicity, neurotoxicity, and plays an important role in cell cycle regulation, differentiation, and apoptotis.[18c–e] Bistramide A displayed IC_{50} of 0.03–0.32 μg/mL for the P388/DOX, B16, HT29, and NSCLC-N6 cell lines,[18f] inhibits Na^+ conductance[18g,h] and is selective toward the activation of a single protein kinase C (PKC) isotype-δ.[18i] These promising biological activities of bistramide A have manifested it as a potential candidate for anticancer therapy.

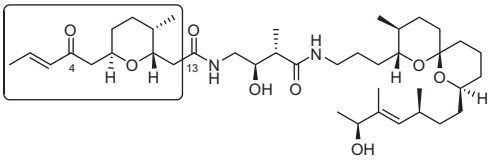
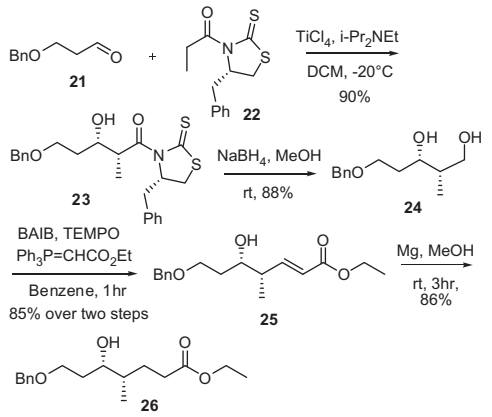


Figure 3. Bistramide A.

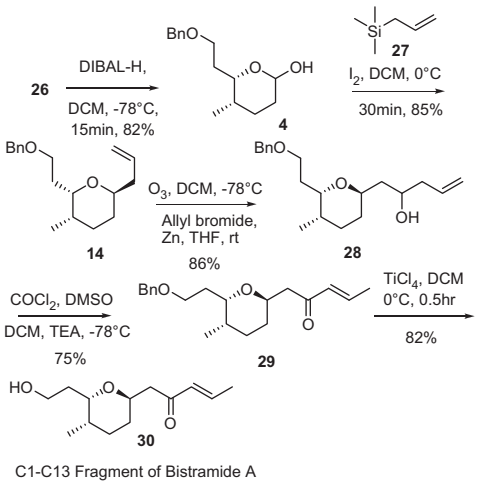


Scheme 2. Synthesis of intermediate **26**.

The first synthesis was achieved by Kozmin and co-workers[19a–c] followed by Crimmins et.al.,[19d] Panek and co-workers[20] and our group.[21a] Structure validation and its synthesis were reported by Peter Wipf et al.[21b,c] and recently Goekjian and co-workers[21d] demonstrated its synthesis and 36(*Z*) isomers. A few research groups have also reported the construction of tetrahydropyran (THP) core[22] in particular.

The synthesis of the THP unit **30** commenced with an asymmetric aldol addition[23,25] reaction of thiazolidinethione propionate to the benzyloxypropanal **21** using $TiCl_4$ and DIPEA as the base. This led to a non Evans syn aldol product **23** in 90% isolated yield. Reductive cleavage of the chiral auxiliary using $NaBH_4$,[24] afforded diol **24**[25] in 88% yield. This diol on selective oxidation in the presence of bis(acetoxy)iodobenzene (BAIB) and 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO), followed by exposure of the crude β-hydroxy aldehyde to ethoxycarbonylmethylene triphenylphosphorane furnished δ-hydroxy-α,β-unsaturated ester **25**[21a,26] in 85% overall yield for the two steps. The double bond of α,β-unsaturated ester was reduced with Mg[27] in methanol to yield the ester **26** in 86% yield (Scheme 2). DIBAL-H reduction of saturated ester afforded the key intermediate lactol **4** in 82% yield.

The lactol **4** was then subjected to the newly developed methodology to furnish the desired C-allylated cyclized product **14**[21c] in 9:1 ratio with 85% isolated yield (Table 1). Then, ozonolysis of terminal alkene with ozone afforded the corresponding intermediate aldehyde, which was directly subjected to an allylation under Barbier conditions[28] to furnish alcohol **28** in 86% overall yield.



Scheme 3. Synthesis of C1–C13 fragment of bistramide A.

The homo allylic alcohol **28** was then oxidized under Swern conditions and excess triethylamine influences the isomerization[29] in one pot and afforded the enone **29**. Finally benzyl deprotection[30] of enone using $TiCl_4$ in methylene chloride gave the enone alcohol **30**[31] (Scheme 3). The pyran intermediate was found identical in all respect to that reported by Crimmins et al.,[19d] and our group.[21a]

In conclusion, a new method for the stereoselective synthesis of *trans*-2,6-disubstituted tetrahydro-2*H*-pyrans has been developed with excellent *trans* selectivity and the approach has been successfully applied in the construction of C1–C13 fragment of bistramide-A in 11 steps with 21.4% overall yield. Further, applications and extensions of the methodology are currently ongoing in our laboratory and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.085.

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31. *General procedure for iodo cyclization:* Iodine (10 mol %) was added to a stirred solution of lactol (1.0 mmol) and allyltrimethyl silane (1.5 mmol) in DCM (5 mL) at 0 °C and allowed to come to room temperature. After completion of the reaction (as indicated by TLC; 30–60 min), the reaction mixture was quenched with saturated solution of NaHCO3 (3–5 mL) and washed with saturated hypo solution. The reaction mixture was extracted with DCM (2 × 5 mL), combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a pale yellow oil, which was purified by silica gel column chromatography using 4–8% ethyl acetate/hexane as eluent to obtain 84–94% of isolated yield of the 2-allyl cyclized product. *(2R,6R)-6-Allyltetrahydro-2H-pyran-2-yl)methoxy)(tert-butyl)dipheny-lsilane*

(***11***): $[\alpha]_D^{25}$ −53.0 (*c* 0.5, $CHCl_3$); IR (KBr, neat): 3072, 3051, 2956, 2932, 2859, 1590, 1462, 1428, 1390, 1251, 1164, 1111, 1086, 1035, 902, 840, 772, 741, 703, 612 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.70–47.64 (m, 4H), 7.44–7.34 (m, 6H), 5.87–5.71 (m, 1H), 5.10–4.97 (m, 2H), 3.90–3.64 (m, 3H), 2.40 (quin, 1H, *J* = 6.99, 13.84 Hz), 2.15 (quin, 1H, *J* = 6.74, 13.83 Hz), 1,621.56 (m, 6H), 1.03–1.07 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.6, 135.3, 129.5, 127.5, 116.4, 71.7, 71.4, 65.0, 38.0, 29.3, 26.8, 26.7, 19.2, 18.2 ppm; ESI-HRMS: calcd for $C_{25}H_{34}O_2Si$ $[M+Na]^+$: 417.2220, found: 417.2190. HPLC ratio 99.3:0.7.

(2S,3S,6R)-6-Allyl-2-(2-(benzyloxy)ethyl)-3-methyltetrahydro-2H-pyran (***14***): $[\alpha]_D^{25}$ −38.66 (*c* 1.5, $CHCl_3$); IR (KBr, neat): 3071, 3031, 2929, 2857, 1642, 1495, 1454, 1367, 1204, 1170, 1096, 997, 911, 698, 611 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38–7.27 (m, 5H), 5.81–5.72 (m, 1H), 5.06–4.96 (m, 2H), 4.49–4.55 (m, 2H), 3.94–3.88 (m, 1H), 3.62–3.48 (m, 3H), 2.24 (quin,1H, *J* = 6.93, 13.86 Hz), 2.11 (quin, 1H, *J* = 7.92, 13.86 Hz), 2.05–1.96 (m, 1H) 1.92–1.82 (m,1H), 1.68–1.56 (m, 3H),1.41–1.24 (m, 2H), 0.80 (d, 3H, *J* = 6.93Hz) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.5, 135.4, 128.3, 127.7, 127.5, 116.3, 73.7, 73.2, 68.6, 67.5, 40.1, 33.0, 30.4, 26.7, 25.7, 16.8 ppm; ESI-HRMS: calcd for $C_{18}H_{26}O_2$ $[M+Na]^+$: 297.1825, found: 297.1851, HPLC ratio 90.5:9.5.

((2S,4S,6S)-2-Allyl-6-(2-(benzyloxy)ethyl)tetrahydro-2H-pyran-4-yloxy)(tert-butyl)dimethylsilane (***17***): $[\alpha]_D^{25}$ +24.64 (*c* 1.4, $CHCl_3$); IR (KBr, neat): 3070, 3031, 2930, 2857, 1722, 1641, 1454, 1361, 1273, 1254, 1219, 1177, 1104. 1006, 913, 836, 773, 711, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.29 (m, 5H), 5.87–5.70 (m, 1H), 5.11–5.01 (m, 2H), 4.49 (m, 2H), 4.06–3.95 (m, 1H), 3.89–3.80 (m, 1H), 3.62–3.49 (m, 2H), 2.64–2.52 (m, 1H), 2.43.2.29 (m, 1H), 2.01–1.90 (m, 1H), 1.87–1.76 (m, 1H), 1.71–1.59 (m, 2H), 1.36–1.25 (m, 1H), 0.89 (s, 9H), 0.05 (S, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.2, 129.5, 128.3, 127.7, 127.5, 116.6, 73.1, 70.6, 66.9, 66.4, 64.9, 40.5, 37.9, 37.1, 35.6, 25.9, 18.3, −4.7 ppm; ESI-HRMS: calcd for $C_{23}H_{38}O_3$ $[M+H]^+$: 391.2663, found 391.2696, HPLC ratio 90.2:9.8.

(E)-1-((2R,5S,6S)-6-(2-Hydroxyethyl)-5-methyltetrahydro-2H-pyran-2-yl)pent-3-en-2-one (***30***): $[\alpha]_D^{25}$: −29.5 (*c* 0.7, $CHCl_3$); IR (KBr, neat): 3448, 2926, 2874, 2856, 1670, 1632, 1442, 1380, 1291, 1201, 1165, 1086, 1057, 970, 911 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.92–6.84 (dq, 1H, *J* = 7.0, 16.0 Hz), 6.15 (dd, 1H, *J* = 7.0, 16.0 Hz), 4.20–4.14 (m, 1H), 3.92 (dt, 1H, *J* = 2.0, 16.0 Hz), 3.75 (t, 2H, *J* = 6.0 Hz), 2.86 (dd, 1H, *J* = 8.0, 16.0 Hz), 2.52 (dd, 1H, *J* = 4.0, 16.0 Hz), 2.01–1.93 (m, 1H), 1.90 (d, 3H, *J* = 2.0, 7.0 Hz), 1.88–1.82 (m, 1H,) 1.78–1.72 (m, 1H), 1.67–1.59 (m, 1H), 1.57–1.40 (m, 2H), 1.37–1.25 (m, 2H), 0.84 (d, 3H, *J* = 6.99 Hz) ppm.^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.7, 143.5, 132.1, 75.4, 66.0, 60.7, 45.5, 32.9, 30.1, 28.5, 26.5, 18.3, 16.3 ppm; ESI-HRMS calcd for $[M+Na]^+$ 249.1461 found 249.1458.