Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 6779–6782
Tetrahedron Letters

1,5-Stereocontrol in reactions of 5-benzyloxy-4-methylpent-2-enyl bromides with aldehydes mediated by Bi(0): synthesis of aliphatic compounds with 1,5-*syn*-related methyl groups

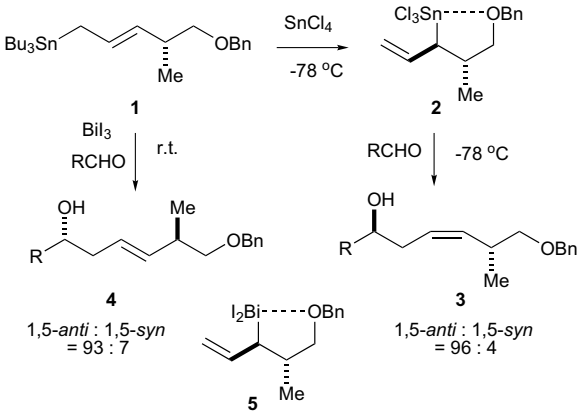
Sam Donnelly,[a] Eric J. Thomas[a,*] and Mark Fielding[b]

[a]*Department of Chemistry, The University of Manchester, Manchester M13 9PL, UK*
[b]*AstraZeneca, Hurdsfield Industrial Estate, Macclesfield, Cheshire SK10 2NA, UK*

Received 2 July 2004; accepted 8 July 2004
Available online 29 July 2004

Abstract—Treatment of the 5-benzyloxy-4-methylpent-2-enyl bromide **6** with the low valent bismuth species formed by reduction of bismuth(III) iodide with zinc powder generates an intermediate, which reacts with aldehydes with useful levels of 1,5-stereocontrol in favour of the 1,5-*anti*-(*E*)-isomers **4**. These products were used to prepared aliphatic compounds with 1,5-*syn*-related methyl groups.

Allylstannanes with heteroatom substituents at the 4-, 5- and 6-positions are transmetallated by tin(IV) halides to give intermediates, which react with aldehydes with effective 1,5-, 1,6- and 1,7-stereocontrol.[1] For example, the 5-benzyloxy-4-methylpent-2-enyl(tributyl)stannane **1** reacts with tin(IV) chloride to give the allyltin trichloride **2**, which gives the 1,5-*anti*-(*Z*)-products **3** on reaction with aldehydes. Recently, it has been found that complementary results are obtained if the transmetallation is carried out using bismuth(III) iodide. Thus addition of the stannane **1** to a suspension of bismuth(III) iodide and an aldehyde in a mixed solvent of acetonitrile and dichloromethane gave the 1,5-*anti*-(*E*)-isomers **4** perhaps via the allylbismuth diiodide **5**.[2]



It would be of interest if these reactions could be carried out by a procedure, which did not use allylstannanes as starting materials.[3] We now report that pent-2-enyl bromides analogous to the stannane **1** react with the low valent bismuth species generated by treatment of bismuth(III) iodide with zinc powder to give intermediates, which give the 1,5-*anti*-(*E*)-products on reaction with aldehydes. These products were used to prepare aliphatic compounds with 1,5-*syn*-related methyl groups.

It has been reported that reduction of bismuth(III) halides with powdered zinc, iron or aluminium generates bismuth(0), which promotes the reaction of allylic bromides and iodides with aldehydes to give homoallylic alcohols.[4] Following the published procedure, a suspension of powdered zinc and a solution of bismuth(III) iodide in tetrahydrofuran was stirred at room temperature for 1 h. Benzaldehyde and the (4*R*)-5-benzyloxy-4-methylpent-2-enyl bromide **6**[5,6] were then added and the mixture heated under reflux for a further 2 h. After cooling, filtration and chromatography on silica

* Corresponding author. Tel.: +44-0161-2754609; fax: +44-0161-2754622; e-mail: tetlet@man.ac.uk

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.07.035

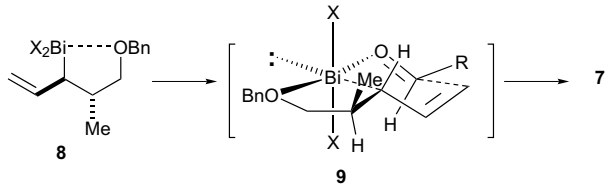
gel gave a good yield of the 1,5-*anti*-(*E*)-alcohol **4a** inseparable from its 1,5-*syn*-(*E*)-diastereoisomer **7a**, ratio 96:4 (83%). A small amount, ca. 5%, of the less polar 1,5-*anti*-(*Z*)-diastereoisomer **3a** was also obtained (Scheme 1).

Structures were assigned to the products **3a**, **4a** and **7a** by comparison with authentic samples.[2] The absolute configuration of the hydroxyl group in the major 1,5-*anti*-(*E*)-isomer **4a** was confirmed by comparison of the ^{1}H NMR spectra of its (*R*)- and (*S*)-*O*-acetyl mandelates.[7]

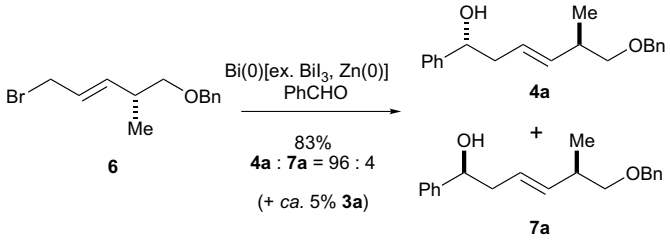
Analogous bismuth(0) mediated reactions of the pentenyl bromide **6** with a range of aldehydes were investigated. In all cases useful stereoselectivity in favour of the 1,5-*anti*-(*E*)-stereoisomers **4** was obtained, see Table 1.[8]

Mechanistic details of these reactions are not clear. Both the zinc powder and the bismuth(III) iodide are required since if either were omitted, no reaction took place. Of interest is the use of very different reaction conditions for the bismuth mediated reactions from those used for the tin(IV) halide promoted reactions of the allylstannanes. In the latter reactions, which are carried out at −78 °C, it is necessary to effect transmetallation of the allylstannane before addition of the aldehyde to avoid the formation of regioisomers via Lewis acid catalysed reactions of the aldehyde with the allylstannane.[1] However, in the reactions involving transmetallation of the allylstannane **1** with bismuth(III) iodide, or in the bismuth(0) induced reactions of the pentenyl bromide **6**, the allylic reagent and the aldehyde were added simultaneously to the bismuth reagent. Prior formation of the reactive allyl metal species is not required. Moreover, the similarity, in particular the regioselectivity, of the products from the bismuth(III) iodide promoted reactions of the allylstannane **1** and the bismuth(0) induced reactions of the pentenyl bromide **6**, suggests that analogous intermediates are involved. The allyl bismuth intermediates must therefore be undergoing 1,3-migration prior to reaction with the aldehyde.

The direct, oxidative insertion of bismuth(0) into the C–Br bond of the pentenyl bromide should not give an intermediate allylbismuth dihalide directly, but disproportionation reactions are possible. Therefore, it may be that an allylbismuth dihalide, for example, **8** (X = I, Br), reminiscent of that proposed for the bismuth(III) iodide promoted reaction of the allylstannane **1**,[2] is involved, and reacts with the aldehyde via a six-membered cyclic transition state, for example, **9**, in which the group next to the bismuth has adopted the equatorial position so leading to the formation of the (*E*)-double-bond. This contrasts with the reactions of the allyltin trichlorides, for example, **2**, formed by transmetallation of allylstannanes by tin(IV) halides. In these cases, (*Z*)-double-bond formation is preferred.[1]

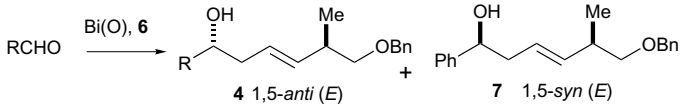


Notwithstanding the mechanistic dichotomy, the use of the pentenyl bromide **6** rather than the allylstannane **1** in



Scheme 1. Bismuth(0) mediated reaction between bromide **6** and benzaldehyde.

Table 1. Bi(0) mediated reactions between aldehydes and the pent-2-enyl bromide **6**

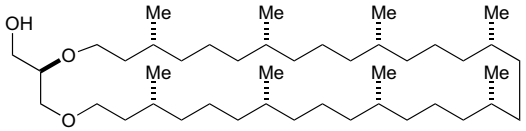


Aldehyde (R)	Major product[a]	Yield (%)[b]	1,5-*anti*:1,5-*syn*
Ph	**4a**	83	96:4
n-Pr	**4b**	92	93:7
i-Pr	**4c**	82	95:5
MeCH=CH	**4d**	86	93:7
$TBSOCH_2$	**4e**	66	95:5
$TBSOCH_2CH_2$	**4f**	63	95:5

[a] In addition to the mixture of *anti*- and *syn*-(*E*)-products **4** and **7**, approximately 5% of less polar (*Z*)-products were also isolated.
[b] Yield corresponds to the mixture of **4** + **7**.

these stereoselective reactions with aldehydes is of interest since separation problems associated with the removal of the organotin side-products are avoided.

To show an application of this chemistry in synthesis, compounds with 1,5-*syn*-methyl bearing stereogenic centres were identified as interesting targets. Such fragments are found in a range of natural products including terpenoids and lipids, for example, **10**, found in the membranes of *Archaea* bacteria.[9] Since methylcuprates are known to react with alkyl toluene *p*-sulfonates with inversion of configuration,[10] the 1,5-*anti*-(*E*)-products from the pentenyl bromide—aldehyde reactions would appear to be suitable precursors for *syn*-1,5-dimethyl compounds.



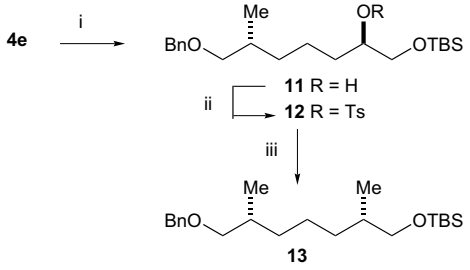
10

To avoid competing rearrangements of the homoallylic toluene *p*-sulfonate, the 1,5-*anti*-(*E*)-product **4e** was reduced using diimide to give the saturated alcohol **11**, which was converted into its toluene *p*-sulfonate **12**. Reaction of this with a higher order cuprate prepared from methyllithium and copper(I) cyanide[10] in toluene as solvent gave the required *syn*-2,6-dimethylheptane-1,7-diol derivative **13** in a 73% yield, Scheme 2, together with a small amount of an elimination product, which was conveniently removed by oxidation of the mixture of crude products using osmium tetraoxide.

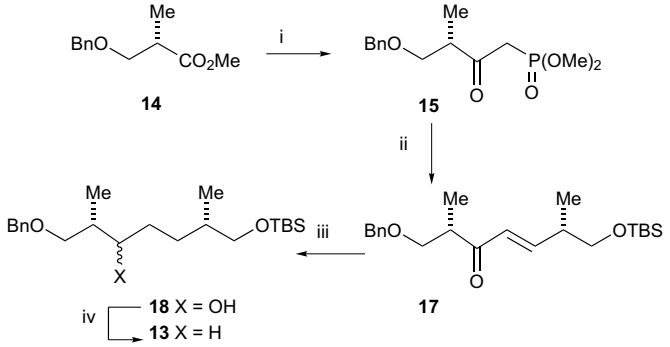
To check the *syn*-stereochemistry assigned to the dimethylheptane **13**, an authentic sample was made by an established route, see Scheme 3.[11] The ketophosphonate **15** was prepared from methyl (2*S*)-3-benzyloxy-2-methylpropanoate **14** and condensed with (2*R*)-2-methyl-3-*tert*-butyldimethylsilyloxypropanal **16** to give the enone **17**. This was reduced using an excess of sodium borohydride to give the saturated alcohol **18** as a mixture of diastereoisomers, which was converted into the *syn*-2,6-dimethylheptane **13** using a Barton procedure. For comparison a mixture of **13** and its 2,6-*anti*-diastereoisomer was also prepared by this route using the racemic 2-methyl-3-*tert*-butyldimethylsilyloxypropanal. Comparison by GLC of the *syn*-2,6-dimethylheptane **13** with the sample prepared from the aldehyde **16** confirmed the assigned *syn*-stereochemistry. Comparison with the mixture of diastereoisomers prepared using the racemic aldehyde confirmed that the 1,5-*syn*:1,5-*anti* ratio in the sample of the dimethylheptane **13** prepared from the alcohol **4e** was ca. 94:6. This also confirmed the 1,5-*anti*-configuration assigned to the alcohol **4e**.

Finally, the *syn*-2,6-dimethylheptane **13** was incorporated into a synthesis of the all *syn*-2,6,10,14-tetramethyl-15-*tert*-butyldimethylsilyloxypentadecan-1-ol **25** an advanced precursor for a synthesis of the membrane lipid **10**, see Scheme 4.

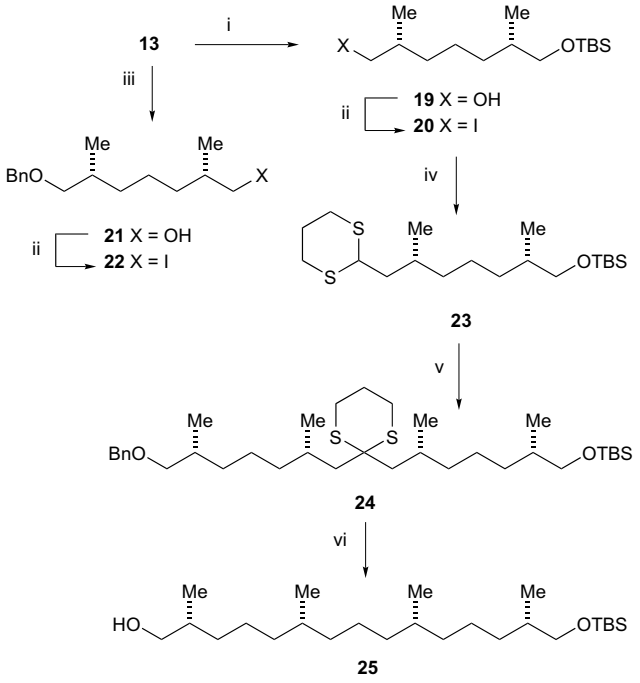
Selective deprotection of the *syn*-2,6-dimethylheptane-1,7-diol derivative **13** gave the alcohols **19** and **21**, which were converted into the corresponding iodides **20** and **22**. Alkylation of dithiane, first with the iodide **20** and then with **22**, gave the bis-alkylated dithiane **24**, which on treatment with Raney nickel gave the monoprotected all *syn*-2,6,10,14-tetramethylpentadecane-1,15-diol derivative **25**. The structure of **25** was consistent with its spectroscopic data with the configuration being assigned on the basis of its synthesis from the *syn*-dimethylheptane



Scheme 2. Reagents and conditions: (i) $TsNHNH_2$, NaOAc (92%); (ii) TsCl, DMAP (90%); (iii) 2 equiv MeLi, CuCN, toluene, 0 °C, 5 h, then OsO_4 (cat.), NMO (73%).



Scheme 3. Reagents and conditions: (i) BuLi, $MeP(O)(OMe)_2$ (88%); (ii) $Ba(OH)_2$, (2*R*)-$TBSOCH_2CHMe{\cdot}CHO$ **16** (84%); (iii) $NaBH_4$ (70%); (iv) a. PhOC(S)Cl (82%), b. Bu_3SnH, AIBN (90%).



Scheme 4. Reagents and conditions: (i) H_2, Pd/C (98%); (ii) I_2, PPh_3, imid (**20**, 96%:**22**, 94%); (iii) TBAF (98%); (iv) *n*-BuLi, dithiane (86%); (v) *n*-BuLi, **22** (78%); (vi) Raney Ni (94%).

13. Since **13** contains about 5% of its *anti*-diastereoisomer, **25** must contain about 10% of minor diastereoisomers, but these could not be separated and were not detected by NMR.

This work has reported a 'tin-free' procedure for 1,5-stereocontrol in reactions between an allylmetal derivative and aldehydes, together with a stereoselective synthesis of open-chain compounds with *syn*-related 1,5-dimethyl substituents.

Acknowledgements

We thank AstraZeneca for a studentship (to S.D.) and Somhairle MacCormick for preparing the enone **17**.

References and notes

1. Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1997**, 411.
2. Donnelly, S.; Thomas, E. J.; Arnott, E. A. *Chem. Commun.* **2003**, 1460.
3. Recently a procedure for 1,6-stereocontrol in indium mediated reactions of 5-hydroxypropargyllic bromides and aldehydes was disclosed, see: Miao, W.; Lu, W.; Chan, T. H. *J. Am. Chem. Soc.* **2003**, *125*, 2412.
4. Wada, M.; Ohki, H.; Akiba, K.-Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1738.
5. The bromide **6** was prepared from the corresponding alcohol (Ref. 6) using CBr_4, Ph_3P.
6. Carey, J. S.; Thomas, E. J. *Synlett* **1992**, 585.
7. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. L.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. J. *Org. Chem.* **1986**, *51*, 2370.
8. *Representative procedure for the bismuth(0) mediated reaction between bromide* **6** *and an aldehyde*: activated zinc powder (31 mg, 0.476 mmol) was suspended in a solution of bismuth(III) iodide (248 mg, 0.42 mmol) in tetrahydrofuran (1.5 cm^3) and the mixture stirred at room temperature for 1 h during which time the grey suspension turned black. A solution of the pentenyl bromide **6** (75 mg, 0.28 mmol) in tetrahydrofuran (0.5 cm^3) and benzaldehyde (29 μL, 0.28 mmol) were added and the resulting mixture heated under reflux for 2 h. After cooling and concentration under reduced pressure, the residue was subjected to flash chromatography on silica being eluted with light petroleum–ether (4:1) to give a mixture of the alcohols **4a** and **7a** (69 mg, 83%) as a colourless oil (found: $[M = NH_4]^+$, 314.2118. $C_{20}H_{28}NO_2$ requires *M*, 314.2120); υ_{max}/cm^{-1} 3424, 3029, 2857, 1494, 1453, 1361, 1201, 1091, 92 and 737; δ_H ($CDCl_3$, 300 MHz): 1,5-*anti*-(*E*)-isomer **4a** 1.14 (3H, d, *J* 7, 5-CH_3), 2.55 (3H, m, 2-H_2 and 5-H), 3.34 (2H, m, 6-H_2), 4.55 (2H, s, $PhCH_2O$), 4.70 (1H, dd, *J* 8 and 5, 1-H), 5.54 (2H, m, 3-H and 4-H) and 7.36 (10H, m, ArH); for the 1,5-*syn*-(*E*)-isomer **7a** 1.15 (3H, d, *J* 7, 5-CH_3); δ_C 17.1, 32.3, 38.5, 73.0, 73.2, 74.6, 125.6, 127.1, 127.6, 127.8, 128.2, 128.5, 136.7 and 144.7; *m/z* (CI) 314 ($[M+NH_4]^+$, 22%), 296 (M^+, 50), 279 (74), 261 (24) and 173 (38).
9. (a) Montenegro, E.; Gabler, B.; Paradies, G.; Seemann, M.; Helmchem, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2419; (b) Eguchi, T.; Ibaragi, K.; Kakinuma, K. *J. Org. Chem.* **1998**, *63*, 2689.
10. Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005.
11. Mulzer, J.; Berger, M. *Tetrahedron Lett.* **1998**, *39*, 803.