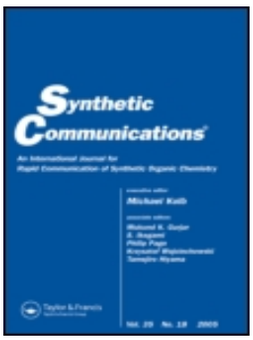

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A PRACTICAL, STEREOSELECTIVE SYNTHESIS OF (*E*)- AND (*Z*)-2-BROMO-2-PENTENES

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ABSTRACT: A short, stereoselective preparation of (*E*)-2-bromo-2-pentene and (*Z*)-2-bromo-2-pentene is described starting from *trans*-2-methyl-2-pentenoic acid.

INTRODUCTION

As part of our synthetic studies toward asteltoxin, we required a stereoselective synthesis of a trisubstituted alkenyllithium or the corresponding Grignard reagent. In particular, a convenient, preparative-scale route to (*Z*)-2-lithio-2-pentene (**1a**) was necessary to further streamline our synthesis of asteltoxin.[1] While this alkenyllithium reagent was previously prepared by transmetalation of the vinylstannane **1b** derived from acetone trisylhydrazone,[2] we found that the requisite series of transformations gave capricious results and that the resulting product **1b** was invariably contaminated by impurities which were difficult to remove. Herein we report a short, practical synthesis of (*E*)-2-bromo-2-pentene (**1c**), as well as (*Z*)-2-bromo-2-pentene (**2**), which is amenable to a large-scale preparation and serves as a convenient precursor of the required reagent.[3]

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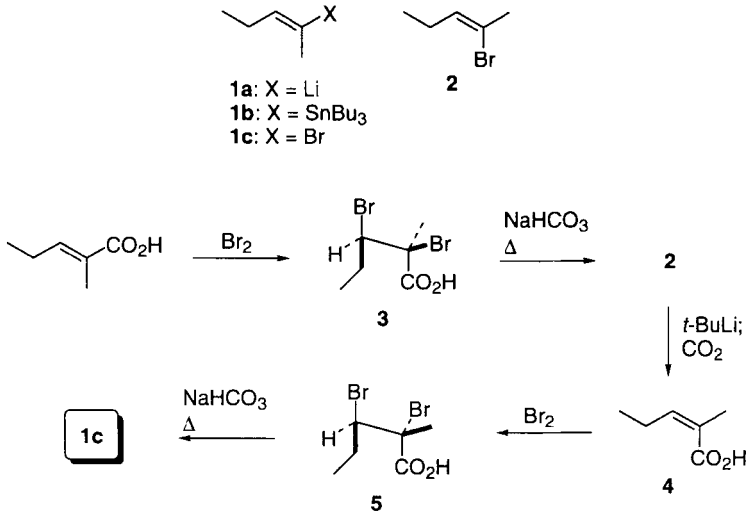
RESULTS AND DISCUSSION



A cursory evaluation of existing methods suggested that hydrozirconation of 2-pentyne with the Schwartz reagent under equilibrating conditions and subsequent trapping with a suitable electrophile might provide a most expedient entry to **1c**.[4] Despite considerable experimentation, however, a mixture of two regioisomers was obtained under all reaction conditions.[5] Other known methods for preparing trisubstituted bromoalkenes, such as the bromination–desilylbromination sequence of vinylsilanes[6] or Wittig olefination,[7] did not offer a convenient synthetic entry. On the other hand, decarboxylative *trans* elimination of α,β-dibromoalkanoic acids, which has largely been confined to the preparation of disubstituted vinyl bromides,[8] could provide an efficient, stereospecific route to the target bromoalkenes. Thus, bromination of commercially available *trans*-2-methyl-2-pentenoic acid at -78 °C gave the *erythro* dibromide **3** in quantitative yield. Subsequent elimination of **3** was then effected under the conditions ($NaHCO_3$, DMF, 65 °C) developed by

Norris[8d] to afford the *Z*-bromide **2** in 83% yield. Stereospecific halogen-lithium exchange with 2 equiv of *tert*-BuLi, followed by treatment with CO_2, produced *cis*-2-methyl-2-pentenoic acid (**4**) in 70% yield.[9] Finally, reiteration of the bromination–decarboxylative elimination sequence on acid **4** furnished the desired *E*-bromide **1c** in 60% overall yield. It is worth mentioning that the vinyl proton (δ 5.85 ppm) in *E*-bromide **1c** is deshielded by the *cis*-vicinal bromine and thus resonates at lower field than in the *Z*-isomer **2** (δ 5.60 ppm).[7]

CONCLUSION

In summary, we have developed an efficient, stereoselective synthesis of trisubstituted vinyl bromides **1c** and **2** by use of the bromination–decarboxylative elimination sequence on the trisubstituted 2-alkenoic acids, which are readily available in the defined configuration. These bromides and/or the resulting organometallic reagents should be useful for the regio- and stereoselective preparation of functionalized trisubstituted alkenes and enynes.[10]

EXPERIMENTAL SECTION

***erythro*-2,3-Dibromo-2-methylpentanoic acid (3).** A solution of *trans*-2-methyl-2-pentenoic acid (5 g, 43.8 mmol) in 88 mL of CH_2Cl_2 was cooled to -78 °C, and 2 equiv of bromine (4.52 mL, 87.7 mmol) was added dropwise. The mixture was then stirred for an additional 1 h at the same temperature and then quenched by addition of aqueous $Na_2S_2O_3$ solution. The organic layer was separated, dried (Na_2SO_4), and concentrated under vacuum to yield 12 g (100%) of the crude product **3** as a light yellow solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3 H), 1.73 (m, 1 H), 1.99 (s, 3 H), 2.43 (qd, J = 7.2, 14.9 Hz, 1 H),

4.50 (d, J = 11.3 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 12.9, 21.7, 26.7, 60.7, 61.8, 174.6.

Z-2-Bromo-2-pentene (2). A suspension of sodium bicarbonate (3.07 g, 36.5 mmol) in 14 mL of DMF was heated to 65 °C, and a solution of the *erythro* dibromide **3** (10 g, 36.52 mmol) in 14 mL of DMF was added slowly over a period of 30–40 min. After heating was continued for an additional period of 30 min (until evolution of CO_2 ceased), the reaction mixture was cooled to room temperature, and 5 mL of water was then added. Extraction with *n*-pentane (8 x 40 mL), washing with water (10 x 10 mL), drying (Na_2SO_4), and removal of the solvent by distillation (oven temperature at 45 °C) afforded 4.5 g (83%) of the *Z*-bromide **2** as a dark brown oil: ^1H NMR (360 MHz, $CDCl_3$) δ 0.99 (t, J = 7.5 Hz, 3 H), 2.14 (m, 2 H), 2.30 (d, J = 1.6 Hz, 3 H), 5.60 (qt, J = 1.6, 6.8 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 12.9, 24.9, 28.7, 121.6, 130.5.

***cis*-2-Methyl-2-pentenoic acid (4).** A solution of the *Z*-bromide **2** (4 g, 26.9 mmol) in 90 mL of ether was cooled to -78 °C, and *tert*-butyllithium (34.8 mL of 1.7M pentane solution, 59.1 mmol) was added dropwise. The mixture was stirred for an additional period of 40 min, and then transferred via cannula to dry ice which had been placed in a 500 mL, two-neck RB flask. The reaction mixture was allowed to slowly warm to -20 °C, quenched by addition of 1N HCl solution, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude acid. For purification, the crude acid was treated by dilute aqueous $NaHCO_3$ solution. The aqueous layer was washed twice with ether, and then acidified to pH 3 with 1N HCl solution. Extraction with ether gave 2.1 g (70%) of the acid **4** of sufficient purity for the next step as a light brown oil: ^1H NMR[9] (360 MHz, $CDCl_3$) δ 1.02

(t, J = 7.5 Hz, 3 H), 1.91 (br d, J = 1.3 Hz, 1 H), 2.53 (apparent quintet, J = 7.5 Hz, 2 H), 6.09 (qt, J = 1.3, 7.5 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.8, 20.4, 23.2, 125.6, 148.3, 173.4.

***threo*-2,3-Dibromo-2-methylpentanoic acid (5).** A solution of *cis*-2-methyl-2-pentenoic acid (**4**) (3.4 g, 29.8 mmol) in 60 mL of CH_2Cl_2 was cooled to -78 °C, and 1.5 equiv of bromine (2.3 mL, 44.7 mmol) was added dropwise. The mixture was then stirred for an additional 1 h at the same temperature and then quenched by addition of aqueous $Na_2S_2O_3$ solution. The organic layer was separated, dried (Na_2SO_4), and concentrated under vacuum to yield 7 g (86%) of the crude product **5** as a light yellow oil: ^1H NMR (360 MHz, $CDCl_3$) δ 1.15 (t, J = 7.5 Hz, 3 H), 1.85-2.05 (m, 2 H), 2.05 (s, 3 H), 4.32 (dd, J = 2.4, 10.5 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.5, 25.4, 29.1, 63.2, 63.9, 174.8.

***E*-2-Bromo-2-pentene (1c).** A suspension of sodium bicarbonate (1.44 g, 17.2 mmol) in 6 mL of DMF was heated to 65 °C, and a solution of the *threo* dibromide **5** (4.7 g, 17.1 mmol) in 9 mL of DMF was added slowly over a period of 30–40 min. After heating was continued for an additional period of 30 min (until evolution of CO_2 ceased), the reaction mixture was cooled to room temperature, and 3 mL of water was then added. Extraction with *n*-pentane (5 x 30 mL), washing with water (5 x 10 mL), drying (over Na_2SO_4), and removal of the solvent by distillation (oven temperature at 45 °C) afforded the crude product as a dark brown oil. Finally, the Kugelrohr distillation (oven temperature 60–70 °C) provided 1.78 g (70%) of the pure *E*-bromide **1c** as a pale yellow oil: ^1H NMR (360 MHz, $CDCl_3$) δ 1.00 (t, J = 7.5 Hz, 3 H), 2.05 (apparent quint, J = 7.5 Hz, 2 H), 2.21 (d, J = 1.0 Hz, 3 H), 5.85 (qt, J = 1.0, 7.5 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.2, 23.0, 27.0, 118.8, 133.9.

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REFERENCES AND NOTES

1. Raman, J. V.; Lee, H. K.; Vleggaar, R.; Cha, J. K. *Tetrahedron Lett.* **1995**, *36*, 3095-3098.

2. Cooke, M. P. Jr. *J. Org. Chem.* **1982**, *47*, 4963-4968.

3. The metal-halogen exchange reaction is a well-known method for preparing organolithium compounds: Wakefield, B. J. In *Organolithium Methods*; Academic: London, 1988; pp 21-52.

4. Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679-680.

5. Direct addition of the resulting vinylzirconocene chloride intermediate to aldehydes is known to take place readily in the presence of $AgAsF_6$ or $AgClO_4$: Suzuki, K.; Hasegawa, T.; Imai, T.; Maeta, H.; Ohta, S. *Tetrahedron* **1995**, *51*, 4483-4494. However, coupling with an α,β-epoxy aldehyde proved to be problematic in our hands.

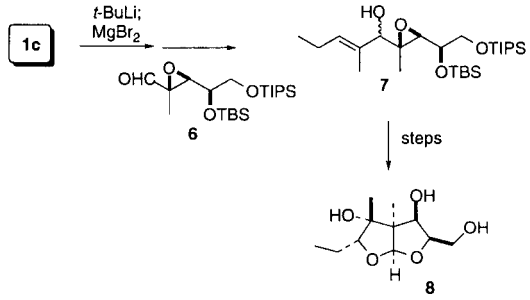
6. (a) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1979**, *44*, 4623-4633. (b) Uchida, K.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1977**, *33*, 2987-2992.

7. Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 2833-2838.

8. (a) Barisch, F. *J. prakt. Chem.* **1879**, *20*, 173-188. (b) Braude, E. A.; Coles, J. A. *J. Chem. Soc.* **1951**, 2078-2084. (c) Cristol, S. J.; Norris, W. P. *J. Am. Chem. Soc.* **1953**, *75*, 2645-6. (d) Norris, W. P. *J. Org. Chem.* **1959**, *24*, 1579-1580.

9. The Z-acid **4** was previously prepared in a stereorandom manner: Chan, K. C.; Jewell, R. A.; Nutting, W. H.; Rapoport, H. *J. Org. Chem.* **1968**, *33*, 3382-3385.

10. For example, sequential treatment of **1c** with *tert*-BuLi (2 equiv), $MgBr_2$, and aldehyde **6** afforded, in good yield, the desired adduct **7**, which was converted to the bis(tetrahydrofuran) subunit **8** of asteltoxin: Kim, H.; Cha, J. K. unpublished results.[1]



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