Alkylation of Schöllkopf's bislactim ether chiral auxiliary with 4-bromo-1,2-butadiene

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Stereoselective synthesis of (2R,5S)-5-(2,3-butadienyl)-, (2R,5S)-5-(2,3-butadienyl)-5-(2-propenyl)- and (2R,5R)-5-(2-bromo-2-propenyl)-5-(2,3-butadienyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazines by alkylation of Schöllkopf's bislactim ether chiral auxiliary with corresponding electrophilic alkenyl halides is described.

Key words: Schöllkopf's bislactim ether, 4-bromo-1,2-butadiene, stereoselective alkylation

INTRODUCTION

Schöllkopf's bislatim ether method is one of the most efficient routes for the asymmetric synthesis of new α-amino acids [1–3]. Stereoselective alkylation of chiral bislactim ether reagent, (2S or 2R)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine, with alkenyl halides, *e.g.*, 3-bromo- and 2,3-dibromopropene, 1-bromo- and 1-bromo-3-methyl-2-butene allowed to obtain important intermediates which were used for the preparation of such unique α-amino acids as 5-hydroxylsine, episulfide analogues of L-methionine, etc. [4–9]. In recent years, a methodology for the asymmetric synthesis of conformationally constrained α-amino acids, which includes bisalkenylation or alkenylation-alkynylation of Schöllkopf's bislactim ether reagent, (2R)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine, and the following ring closing metathesis reaction (RCM) has been developed. Bisalkylation of the chiral auxiliary usually is to be effected in a stepwise manner which allows the introduction of two different unsaturated hydrocarbon moieties [10–12]. The RCM reactions were carried out by Grubbs methodology using a carbenoid ruthenium (II) complex as a catalyst [13, 14] .

Substituted allenes are known as versatile synthetic intermediates [15]. Cyclic carbopaladation reaction of allenes is applicable to the synthesis of cyclic compounds of almost any ring size [16–18].

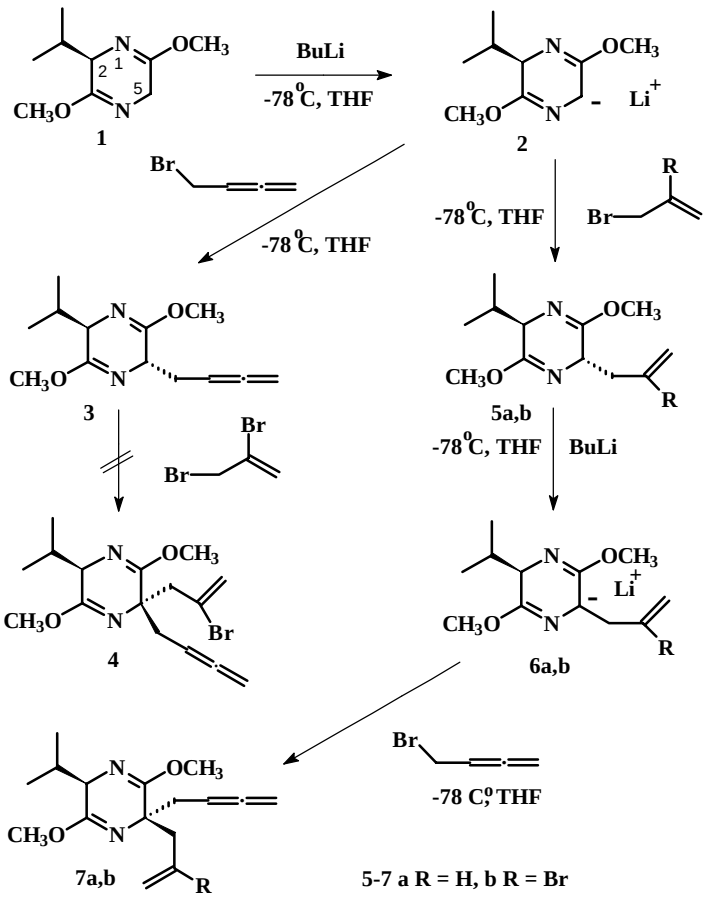
The scope of the present work is an investigation of alkylation of Schöllkopf's bislactim ether auxiliary with 4-bromo-1,2-butadiene in order to synthesize new chiral intermediates possessing the allenic moiety.

RESULTS AND DISCUSSION

The reagent 4-bromo-1,2-butadiene was prepared by the reaction of phosphorus tribromide with 2,3-butadien-1-ol [19]. The alcohol is readily accessible from propargyl chloride [20]. The latter was lithiated and subsequently hydroxymethylated with paraformaldehyde. Treatment of the resultant 4-chloro-2-butyn-1-ol with $LiAlH_4$ gave 2,3-butadien-1-ol.

The reaction of the chiral auxiliary, (2R)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine **1** with 4-bromo-1,2-butadiene, was carried out in accordance with Schöllkopf's method of alkylation [1, 2]. In the first stage of the synthesis the bislactim ether **1** was treated with *n*-butyllithium at –78 °C. Deprotonation at C-5 gave the almost planar dihydropyrazine anion **2** which easily underwent electrophilic attack by 4-bromo-1,2-butadiene.

After routine work-up of the reaction mixture, only the isomer **3** with the substituent in a *trans*-relationship to the isopropyl group was obtained (TLC, NMR). Electrophiles would add to the lithiated bislactim ether in such a way as to minimize steric interactions. Therefore the allenic electrophile attacks preferentially the pyrazine ring *trans* to the isopropyl group, the major product having the structure **3**. The assignment of absolute configuration is in accord with the normal findings in Schöllkopf's asymmetric amino acid synthesis [1–3]. The presen-



ce of the allenic moiety in the product, and therefore the assignment of structure **3**, is evident from the presence of two multiplets of allenic protons in the ^{1}H NMR spectrum, in the regions 4.53–4.59 and 4.94–4.97 ppm.

For the preparation of the dialkylated product **4**, the allenyl derivative **3** was subjected to a second alkylation reaction using 2,3-dibromopropene. This reaction could not be effected presumably in part because of base catalyzed proton abstraction from the methylene carbon of the allenic moiety and subsequent isomerization reactions, or because of steric interference from the vinyl bromo substituent. For dialkylation this problem was overcome by changing the order of alkylation. This operation leads to a target molecule with the opposite configuration at the stereogenic C-5 position. The different stereochemical courses in the above cases will be evident by a comparison of the structures **4** and **7**. In this approach the Schöllkopf's auxiliary **1** was first alkylated with 3-bromo- and 2,3-dibromopropene by the previously described methods [5, 21]. The major products of the reactions were, correspondingly, 5-(2-propenyl)- and 5-(2-bromo-2-propenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazines **5 a, b**. In both cases, the minor isomer can be removed by flash chromatography, but separation is not necessary since the overall stereochemistry in the reaction sequence is determined during the second alkylation step.

Lithiation of the monoalkylated species **5 a, b** was followed by treatment with 4-bromo-1,2-butadiene resulting in the formation of the dialkylated products **7 a, b**. The stereoselectivity in the second alkylation is remarkable as has been found previously in related reactions [10–12]. Only one stereoisomer was observed. As before, the electrophile adds to the pyrazine ring in a trans manner with respect to the isopropyl group. This being so, it is seen that the original stereochemistry at C-5 in the substrate **5**, which was used for the alkylation, is not important since the stereochemistry at C-5 is lost on metallation (**6 a, b**). The d.e. of the products **7 a, b** after the second alkylation step was excellent, in excess of 95%; the chemical yields were in the range 50–60%.

CONCLUSIONS

1. The alkylation of Schöllkopf's bislactim ether chiral auxiliary with 4-bromo-1,2-butadiene proceeds with high diastereoselectivity and acceptable chemical yield.

2. 4-Bromo-1,2-butadiene is an efficient electrophilic reagent for the second stereoselective alkylation of 5-monosubstituted Schöllkopf's bislactim ether species.

EXPERIMENTAL

^{1}H NMR spectra were registered in $CDCl_3$ at 200 MHz with Bruker DPX 200. The ^{13}C NMR spectra were recorded in $CDCl_3$ at 50 MHz with Bruker DPX 200. The mass spectra under electron impact conditions were recorded at 70 eV ionizing potential. The spectra are presented as m/z (% rel. int.).

4-Bromo-1,2-butadiene. To a solution of 2,3-butadien-1-ol (3.0 g, 0.043 mol) in ether (13 ml) containing pyridine (0.26 ml) phosphorus tribromide (4.32 g, 1.52 ml, 0.016 mol) was added dropwise over a period of 45 min at –40 °C. The temperature was maintained for 2 h at – 40 °C, during which time a slow nitrogen flow was introduced. Then the temperature was allowed to rise to 20 °C over 3 h. The reaction was heated and kept at 40 °C for 30 min. The reaction mixture was cooled to 20 °C and poured onto a saturated solution of NaCl (30 ml). The aqueous layer was extracted with ether (3 x 10 ml). The combined organic extracts were dried over $MgSO_4$, the ether removed at at-

mospheric pressure. The residue was distilled at reduced pressure (water pump, b.p. 75–78 °C), to give 2.60 g (46%) of the target product. ^{1}H NMR ($CDCl_3$): δ 3,92 (dt, 2H, J 1.98 Hz, CH_2), 4.90 (dt, 2H, J 6.50 Hz, CH_2), 5.34–5.48 (m, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 30.3 (CH_2), 77.4 (CH), 89.7 (CH_2), 210 (C).

(2R,5S)-5-(2,3-Butadienyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (3). nBuLi (0.90 ml, 2.23 mmol, 2.5 M in hexane) was added to a solution of (R)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine **1** (374 mg, 2.02 mmol) in dry THF (10 ml) under argon at –78 °C. After 20 min, 4-bromo-1,2-butadiene (300 mg, 2.26 mmol) in THF (3 ml) was added dropwise over 20 min. The mixture was left to reach ambient temperature overnight before the reaction was quenched by addition of water (8 ml). The aqueous layer was extracted with ether (3 x 8 ml). The combined ether solutions were dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography using 5% ethyl acetate in hexane as eluent to give 229 mg (48%) of compound **3** as a colorless oil. Found: C, 66.14; H, 8.35. Calculated for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53%. $[\alpha]_D$ = + 42° (c = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.64 (d, J 7.0 Hz, 3H, CH_3), 1.03 (d, J 7.0 Hz, 3H, CH_3), 2.23 (m, 1H, CH), 2.42–2.52 (m, 2H, CH_2), 3.65 (s, 6H, 2 x CH_3O), 3.90 (m, 1H, H-2), 4.07 (m, 1H, H-5), 4.53–4.59 (m, 2H, CH_2), 4.94–4.97 (m, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 16.50 (CH_3), 19.0 (CH_3), 31.68 (CH), 33.50 (CH_2), 52.24 (2 x CH_3O), 55.30 (C-5), 60.80 (C-2), 73.80 (CH_2=), 85.0 (CH=), 162.80 (C), 164.0 (C), 209.7 (=C=). MS (EI): 236 (5.8 M^+), 221 (18), 193 (34), 183 (8), 141 (100), 126 (7), 53 (11).

(2R,5S)-5-(2,3-Butadienyl)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(2-propenyl)pyrazine (7a). nBuLi (0.10 ml, 0.25 mmol, 2.5 M in heptane) was added to a solution of compound **5a** (74 mg, 0.33 mmol) in dry THF (3 ml) under argon at –78 °C. After 40 min, 4-bromo-1,2-butadiene (49 mg, 0.36 mmol) in THF (1 ml) was added dropwise over 10 min. The mixture was kept for 1.5 h at –78 °C and then left for 1 h to reach ambient temperature. A solution of NH_4Cl (10%, 12 ml) was added to the reaction mixture, and the aqueous layer was extracted with ether (3 x 10 ml). The combined ether solutions were dried ($MgSO_4$) and evaporated to dryness. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography using 5% ethyl acetate in hexane as eluent to give 76 mg (63%) of compound **7a** as a colorless oil. Found: C, 68.51; H, 8.58. Calculated for $C_{16}H_{24}N_2O_2$: C, 69.06; H, 8.69%. ^{1}H NMR ($CDCl_3$): δ 0.61 (d, J 7 Hz, 3H, CH_3), 1.03 (d, J 7Hz, 3H, CH_3), 2.16–2.28 (m, 1H, CH), 2.34-2.45 (d, 2H, CH_2), 2.46–2.59 (d, 2H, CH_2), 3.62 (s, 3H, CH_3O), 3.69 (s, 3H, CH_3O), 3.85 (d, 1H, CH), 4.51–4.55 (m, 2H, =CH_2), 4.74–4.81 (m, 1H, CH=), 4.96–5.03 (d, 2H, =CH_2), 5.55–5.68 (m, 1H, CH=). ^{13}C NMR ($CDCl_3$): δ 17.6 (CH_3), 19.9 (CH_3), 31.0 (CH), 40.3 (CH_2), 44.7 (CH_2), 52.4 (CH_3O), 52.7 (CH_3O), 61.1 (C-2), 62.5 (C-5), 73.9 (=CH_2), 85.1 (CH=), 117.9 (=CH_2), 134.8 (= CH_2), 163.3 (C), 163.6 (C), 210.4 (=C=). MS (EI): 276 (1,10 M^+), 261 (7), 233 (15), 223 (45), 193 (15), 181 (100), 53 (11), 41 (15).

(2R,5R)-5-(2-Bromo-2-propenyl)-5-(2,3-butadienyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (7b).). nBuLi (0.15 ml, 0.36 mmol, 2.5 M in hexane) was added to a solution of compound **5b** (100 mg, 0.33 mmol) in dry THF (3 ml) under argon at –78 °C. After 10 min, 4-bromo-1,2-butadiene (66 mg, 0.50 mmol) in THF (1 ml) was added dropwise over 10 min. The mixture was kept at the same temperature for 3 h and then left for 1 h to reach ambient temperature. A water solution of NH_4Cl (10%, 12 ml) was added to the reaction mixture, and the aqueous layer was extracted with ether (3 x 10 ml). The combined ether solutions were dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography using 5% ethyl acetate in hexane as eluent to give 53 mg (46%) of compound **7b** as a colorless oil. Found: C, 52.79; H, 6.29. Calculated for $C_{16}H_{23}BrN_2O_2$: C, 53.09; H, 6.48%. $[\alpha]_D$= –39 (c = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.70 (d, J 6.8 Hz, 3H, CH_3), 1.05 (d, J 6.8 Hz, 3H, CH_3), 2.20–2.42 (m, 3H, CH, CH_2), 2.75 (d, J 13.9 Hz, 1H, CH_2), 3.06 (d, J 13.9 Hz, 1H, CH_2), 3.65 (s, 3H, CH_3O), 3.69 (s, 3H, CH_3O), 3.80 (d, J 3.4 Hz, 1H, CH), 4.53–4.50 (m, 2H, =CH_2), 4.70–4.80 (m, 1H, CH=), 5.48 (d, J 21.1 Hz, 2H, =CH_2). ^{13}C NMR ($CDCl_3$): δ 16.71 (CH_3), 19.63 (CH_3), 30.38 (CH_2), 40.38 (CH), 49.78 (CH_2), 51.88 (CH_3O), 52.40 (CH_3O), 60.76 (C-2), 62.29 (C-5), 73.67 (=CH_2), 84.20 (CH=), 121.17 (=CH_2), 128.09 (C-Br), 161.81 (C), 163.14 (C), 210.22 (=C=). MS (EI): 355 (0.2 M+), 313 (31), 303 (42), 275 (45), 259 (100), 180 (46), 53 (21), 43 (33).

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SCHÖLLKOPF'O CHIRALINIO BISLAKTIMETERIO ALKILINIMAS 4-BROM-1,2-BUTADIENU

S a n t r a u k a

Alkilinant Schöllkopf'o chiralinį bislaktimeterį 4-brom-1,2-butadienu reakcija vyksta stereoselektyviai ir gaunamas (2R,5S)-5-(2,3-butadienil)-2,5-dihidro-3,6-dimetoksi-2-izopropilpirazinas. Minėtą bislaktimeterį pirmiausiai alkilinant 3-bromo- arba 2,3-dibrompropenu, o po to – 4-brom-1,2-butadienu susintetinti (2R,5S)-5-(2-propenil)- ir (2R,5R)-5-(2-brom-2-propenil)-5-(2,3-butadienil)-2,5-dihidro-3,6-dimetoksi-2-izopropilpirazinai.

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АЛКИЛИРОВАНИЕ ХИРАЛЬНОГО БИСЛАКТИМНОГО ЭФИРА ШЕЛКОПФА 4-БРОМ-1,2-БУТАДИЕНОМ

Р е з ю м е

При алкилировании хирального бислактимного эфира Шелкопфа 4-бром-1,2-бутадиеном реакция происходит стереоселективно и образуется (2R,5S)-5-(2,3-бутадиенил)-2,5-дигидро-3,6-диметокси-2-изопропилпиразин. При алкилиро-вании упомянутого бислактимного эфира сначала 3-бром- или 2,3-дибромпропеном, а затем - 4-бром-1,2-бутадиеном синтезированы (2R,5S)-5-(2-пропенил)- и (2R,5R)-(5-(2-бромо-2-пропенил)-5-(2,3-бутадиенил)-2,5-дигидро-3,6-диметокси-2-изопропилпиразины.