Tetrahedron Letters, Vol. 33, No. 51, pp. 7899-7902, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .
Pergamon Press Ltd

Samarium(II) Iodide-Mediated Reductive Cyclization Approach to Total Synthesis of the Insect Sex Attractant (-)-Anastrephin

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Abstract: Intramolecular reductive cyclization of enantiomerically pure γ,γ-differentially C-substituted α,β-unsaturated ester **5** having a terminal aldehyde functionality, was effectively achieved using SmI_2 in THF-HMPA. Starting with the major cyclization product **6**, enantiospecific total synthesis of (-)-anastrephin **1** was completed.

Owing to their potency to create a carbon-carbon bond, reductive coupling reactions mediated by lanthanides such as Sm(II) iodide have been extensively investigated in recent years.[1] Applications of the SmI_2-mediated reductive coupling reactions to substrates having two carbonyl functionalities in the molecules can provide five- and six-membered carbocycles. We have studied currently several approaches to enantiomerically pure carbocycles.[2] Herein, we report result of the SmI_2-mediated intramolecular reductive coupling reaction of a D-glucose-derived substrate such as **5**.[3] The major product obtained by the reductive cyclization **6** could be efficiently transformed into (-)-anastrephin (**1**), an insect sex attracting pheromone.

(-)-Anastrephin **1** (Fig. 1) is one of the insect pheromone isolated from the Caribbean fruit fly *Anastrepha suspensa* Loew[4,5] and also from Mexican fruit fly *Anastrepha ludens* Loew.[4,5] Together with the 4-epimer epianastrephin, the pheromone **1** secreted by the male insects shows an attracting activity against the females. Racemic total syntheses of **1** and epianastrephin were reported by two groups,[6] and both enantiomers of **1** and the 4-epimer were obtained by optical resolution of both racemates.[7] Our synthetic approach to the enantiomerically pure (-)-**1** is summarized in Fig. 1. A key step of our total synthesis is the SmI_2-mediated reductive coupling reaction of a γ,γ-differentially C-substituted α,β-unsaturated ester **5** having a terminal aldehyde functionality, which in turn would be prepared from D-glucose.

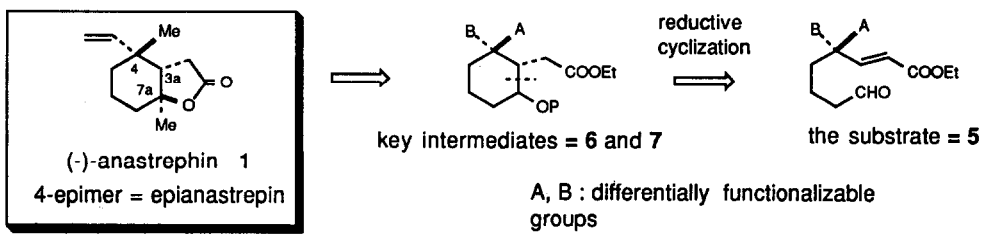
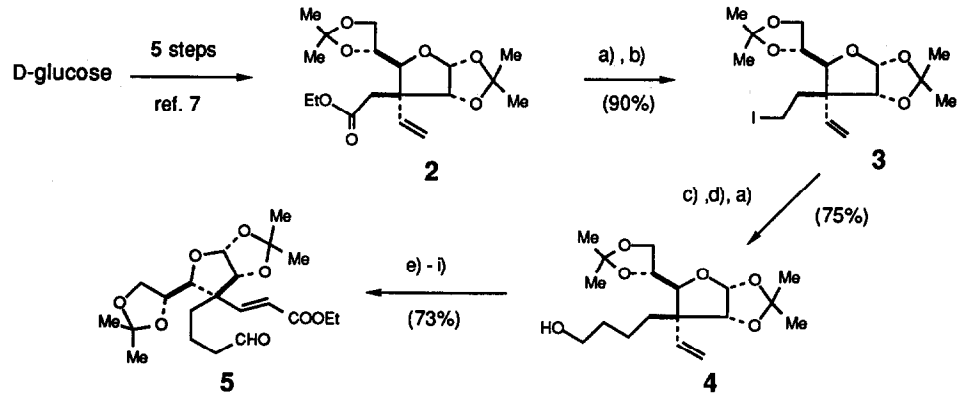


Fig. 1

The preparation of the substrate **5** for the key reductive cyclization was efficiently achieved as shown in Scheme 1. The starting compound **2**, which was readily obtained from D-glucose in a five-step reaction,[8] was converted to a two-carbon elongated compound **4**[9] *via* alkylation of the iodide **3**[9] with dimethyl malonate

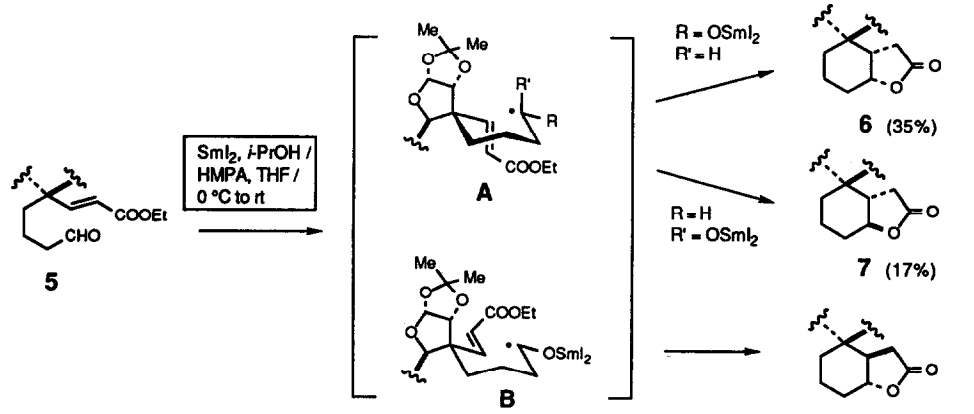
followed by decarboxylation and reduction. Further manipulation of both side chains at the quaternary carbon in **4** provided **5**[9] *via* a Wittig olefination for introduction of the α,β-unsaturated ester functionality.



a) $LiAlH_4$ / THF; b) Ph_3P, DEAD, MeI /THF; c) $CH_2(COOMe)_2$, NaH / THF; d) NaCl / aq. DMSO /160 °C; e) TBDMSCl , imidazole / DMF; f) O_3, then Ph_3P / CH_2Cl_2 / -78 °C; g) $(EtO)_2P(O)CH_2COOEt$, NaH / THF; h) TBAF / aq. THF; i) PCC / MS / CH_2Cl_2.

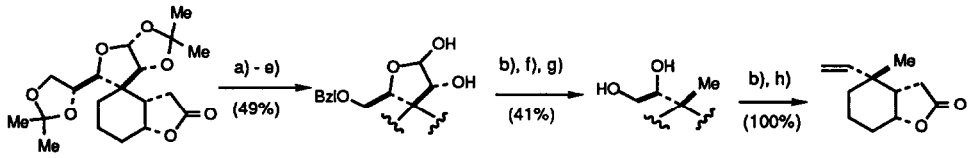
Scheme 1

The SmI_2-mediated reductive cyclization of **5** was best achieved by stirring a solution of **5** in THF at rt in the presence of HMPA (1/10 volume of THF)[10] and 1.5 mol eq. of *i*-PrOH as a proton source. Three coupling products, perhydrobenzofuran derivatives **6**-**8**[9] were obtained in 35%, 17%, and 14% yields, respectively (Scheme 2). The structure of each product was ascertained by ^1H NMR analysis of chemically modified derivatives. A plausible mechanism of the reductive cyclization of **5** is illustrated in Scheme 2. In the initially formed ketyl radicals **A** and **B**, the α,β-unsaturated ester part disposes axially for **A** or equatorially for **B** in the chairlike transition state. Comparing two transition states, contribution of the thermodynamically less stable **A** leading to **6** and **7** seems to be advantageous by reason that the other conformation **B** may encounter with a non-bonded interaction between the isopropylidene group. Also, preferential formation of **6** indicates that the alkoxide group ($OSmI_2$) in **A** favorably disposes equatorially to avoid a 1,3-diaxial interaction.



Scheme 2

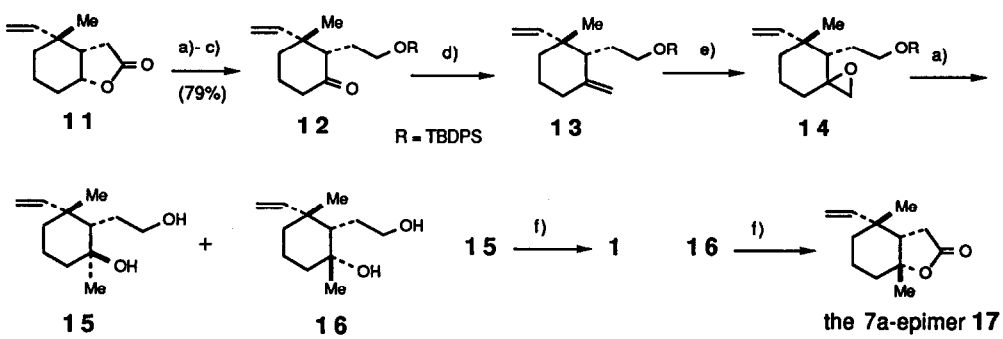
The total synthesis of (-)-**1** was started with the major coupling product **6** (Scheme 3). Differential functionalization of two side chains at the asymmetric quaternary carbon in **6** (=the furanose part) provided **11**[9] uneventfully [1) selective deisopropylidenation, 2) cleavage of the diol followed by reduction and protection as a benzyl ether, 3) hydrolysis of the remaining isopropylidene group (=formation of **9**[9]), 4) $NaIO_4$ oxidation, dithioacetal formation followed by desulfurization concurred with debenzylation (=formation of **10**[9]), and 5) conversion of the diol to a vinyl group]. We also achieved transformation of the furanose part into geminal methyl and vinyl groups with configuration opposite to **11** by change of the functional group transformation. Consequently, total synthesis of epianaetrephin (the 4-epimer of **1**) would be possible.



a) 1N aq. HCl / THF / 5 °C; b) $NaIO_4$ / aq. MeOH; c) $NaBH_4$ / MeOH; d) BzlBr, NaH / DMF;
e) 60% aq. CF_3COOH / 5 °C; f) EtSH, conc. HCl / -15 °C; g) Raney Ni / EtOH / reflux; h) $Ph_3P{=}CH_2$ / THF.

Scheme 3

The remaining stereogenic center, C-7a of **1**, was introduced as shown in Scheme 4. The lactone part of **11** was once reduced and the resulting diol was selectively protected as a silyl ether, then the secondary hydroxyl group was oxidized to a cyclohexanone derivative **12**.[9] Oshima-Nozaki olefination[11] of **12** provided an exo-methylene derivative **13**[9] in 88% yield.[12] We were pleased to find that epoxidation of **13** with *m*-chloroperbenzoic acid proceeded regioselectively to provide mono epoxy derivative **14**[9] in 57% yield although the stereoselectivity was not observed (33% of **13** was recovered). $LiAlH_4$-reduction of the mixture **14** concurred with desilylation to give **15**[9] and **16**[9] in 57% and 33% yields, respectively, which were readily separated by silica gel chromatography. Although the stereoselectivity in the epoxidation of **13** was not superior, we were encouraged by this result because direct nucleophilic methyl group addition to the cyclohexanone **12** with MeLi gave the undesired β-methyl derivative exclusively.



a) $LiAlH_4$ / THF / reflux; b) TBDPSCl, imidazole / DMF; c) PCC / MS / CH_2Cl_2; d) Zn-CH_2Br_2-$TiCl_4$ / THF-CH_2Cl_2;
e) *m*-CPBA, $NaHCO_3$ / CH_2Cl_2; f) PCC / MS / CH_2Cl_2.

Scheme 4

Finally, exposure of compound **15** to PCC provided (-)-anastrephin **1** in 67% yield. Under these oxidation conditions, lactonization accompanied. Mp and $[\alpha]_D$ of the synthetic **1** coincided with those reported.[7b] ^1H (270 MHz) and ^{13}C NMR (100 MHz) of the synthetic **1** were in complete accord with the reported data for the (+)-antipode.[7b] Analogously, compound **16** was converted to (-)-7a-epianastrephin **17** [mp 36.5-38.5 °C, $[\alpha]_D$ -55.1° (*c* 0.28, *n*-hexane)] in 83% yield.

The present work demonstrates the potency of the SmI_2-mediated reductive cyclization, which was realized using the carbohydrate derivative **5**, as a tool for structurally crowded six-membered carbocycles formation. The enantiospecific total synthesis of (-)-anastrephin **1** was achieved, and the stereocongeners of **1** would be obtainable from the other cyclization product **8**.

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9. All new compounds described herein were fully characterized by spectral means (IR, ^1H NMR) and gave satisfactory chemical composition by combustion analysis or exact (high-resolution) mass spectrum.
10. When the cyclization was performed without HMPA, significant amount of unlactonized forms of **6-8** and uncyclized products, which were produced by reduction of the aldehyde functionality, were isolated.
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12. When Wittig reaction of the cyclohexanone **12** was performed with $Ph_3P{=}CH_2$ (salt free), nearly 4: 1 mixture of **13** and its epimer at carbon bearing the 2-(*tert*-butyldiphenylsiloxy)ethyl group was obtained as an inseparable mixture.

(Received in Japan 24 August 1992)