Pergamon

Tetrahedron Letters 40 (1999) 5931–5934

TETRAHEDRON
LETTERS

A Novel Synthesis of *trans*-Enynes from Substituted Tetrahydropyrans

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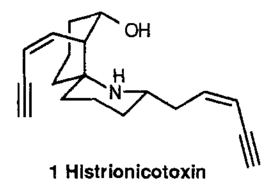
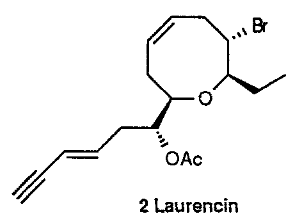
Received 12 April 1999; accepted 15 June 1999

Abstract: A novel method for the synthesis of *trans*-enynes is described, which relies on a butyllithium induced ring scission of 3-bromo-2-ethynyltetrahydropyrans. © 1999 Elsevier Science Ltd. All rights reserved.

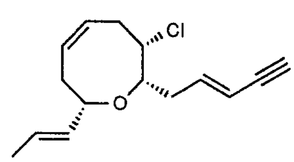
The enyne subunit is a common functional entity in many natural products, including histrionicotoxin (**1**),[1] which bears two *cis*-enyne containing side-chains, and laurencin (**2**)[2] and (–)-laurenyne (**3**),[3] both of which contain *trans*-enyne functionality.



1 Histrionicotoxin

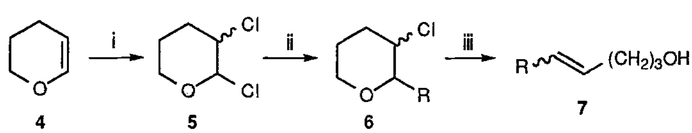


2 Laurencin



3 (–)-Laurenyne

Crombie and co-workers have shown that ring-cleavage of α-alkyl-β-halogenotetrahydropyrans (**6**) and furans provides a very good means of synthesis of *Z*/*E* olefinic mixtures (**7**) as shown in Scheme 1.[4,5,6] Sodium and samarium iodide were used in order to accomplish this transformation, to obtain *Z*/*E* olefins, dienes and styrenes.



Scheme 1. *Reagents*: i, Cl_2; ii, RMgX; iii, Na

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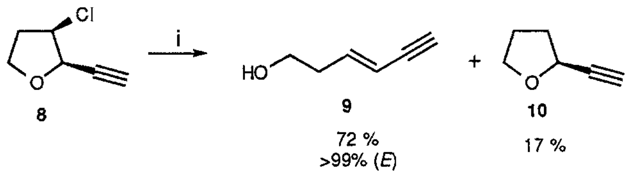
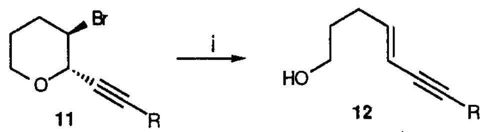
PII: S0040-4039(99)01176-4

In 1994, Crombie and Rainbow reported on the stereoselective synthesis of (Z)- and (E)-enynes using samarium iodide for the ring-scission of α-acetylenic-β-halogenoethers.[7] It was observed that acetylenic tetrahydrofurans (**8**) provided exclusively (E)-enynes (**9**), together with a small quantity of reduction product (**10**) (Scheme 2) whereas acetylenic tetrahydropyrans reacted with samarium iodide to afford predominantly (Z)-enynes.



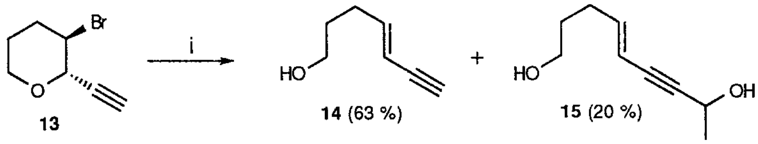
Scheme 2. *Reagents*: i, SmI_2

We now wish to report on an extension of this work, and specifically on the synthesis of (E)-enynes (**12**) from substituted tetrahydropyrans (**11**), using *n*-butyllithium or cobaloxime(I)[8] as depicted in Scheme 3.



Scheme 3. *Reagents*: i, *n*-BuLi or cobaloxime(I)

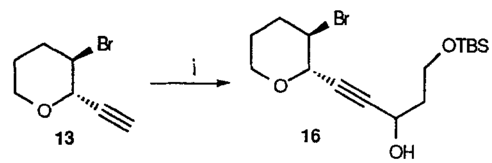
trans-3-Bromo-2-ethynyltetrahydropyran (**13**)[9] was prepared by treatment of 2,3-dibromotetrahydropyran[10] with ethynylmagnesium bromide. Since we were initially interested in functionalising the acetylene moiety, we examined the reaction of the acetylenic bromide with an excess of *n*-butyllithium and acetaldehyde at low temperature. It was found that halogen-metal exchange occurred, followed by stereoselective ring-opening of the tetrahydropyran, to afford the (E)-enynes (**14**) and (**15**) in a ratio of 3:1 (Scheme 4).



Scheme 4. *Reagents*: i, *n*-BuLi, CH_3CHO, THF, –78°C

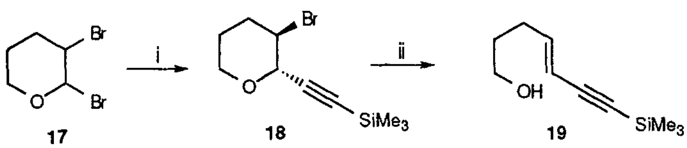
The use of a more complex aldehyde, such as 3-[(*tert*-butyldimethylsilyl)oxy]propanal provided the substituted acetylenic dihydropyran in low yield, together with the ring-opened *E*-alkene (2:1 ratio; 35 % overall). The use of a non-nucleophilic base such as lithium diisopropylamide (LDA) provided the propargylic alcohol (**16**) as the exclusive product (45 %), as expected (Scheme 5).

We wished to explore further the reaction leading to the ring-opened *trans*-enyne, and examined the use of cobalt chemistry.



Scheme 5. *Reagents*: i, LDA, $TBSOCH_2CH_2CHO$, THF, –78°C

The silylacetylene (**18**) was prepared in moderate yield by treatment of 2,3-dibromotetrahydropyran (**17**) with the anion of trimethylsilylacetylene at –78°C. *In situ* preparation of the cobaloxime(I) from cobalt(II) chloride hexahydrate, dimethylglyoxime, pyridine and sodium hydroxide under an hydrogen atmosphere, followed by addition of (**18**) afforded the *trans*-enyne (**19**) as the exclusive isolable product in 45 % yield (Scheme 6).[11]



Scheme 6. *Reagents*: i, *n*-BuLi, trimethylsilylacetylene, Et_2O, –78°C (43 %); ii, $CoCl_2{\cdot}6H_2O$, dimethylglyoxime, Py, NaOH, H_2 (45 %)

In conclusion, we have described a selective method for the preparation of *trans*-enynes from acetylenic tetrahydropyrans using cobaloxime(I), which complements the previous work reported by Crombie and Rainbow, who obtained selectively *cis*-olefins by treatment with samarium iodide.

ACKNOWLEDGEMENTS

The Ministry of Turkish Education is gratefully acknowledged for generous financial support (B.K.).

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11. *Typical procedure*: to a degassed (N_2) solution of cobalt(II) chloride 6-hydrate (31 mg, 0.13 mmol), dimethyl glyoxime (31 mg, 0.26 mmol) and methanol (10 ml) was added pyridine (0.01 ml, 0.13 mmol), followed by aqueous 10 M sodium hydroxide solution (0.025 ml, 0.25 mmol) which resulted in the formation of a black solution. Degassing (N_2) was continued for 10 min, and then hydrogen was introduced into the reaction mixture (balloon). After 5 min, 3-bromo-2-(2-trimethylsilylethynyl) tetrahydropyran (34 mg, 0.13 mmol) was added, and the reaction mixture was then stirred for 3 h under an atmosphere of hydrogen. The mixture was poured into distilled water, extracted with diethyl ether and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by flash column chromatography (silica, 50 % petroleum ether/diethyl ether, R_f=0.3) to afford the trans-enyne as a pale yellow oil (10 mg, 42 %). δ_H (300 MHz, $CDCl_3$, Me_4Si) 6.01-6.10 (dt J=15.9, 7.1 Hz, 1H), 5.30-5.40 (d J=15.9 Hz, 1H), 3.45-3.52 (t J=6.4 Hz, 2H), 2.00-2.10 (m, 2H), 1.50 (quint J=6.9 Hz, 2H) ppm; δ_C (75 MHz, $CDCl_3$, Me_4Si) 29.40, 31.52, 62.18, 93.03, 103.87, 110.28, 145.22 ppm; ν_{max} (film) 3330 (br OH str) 2851 (m, CH), 2332 (w, acetylene), 1628 (w, alkene), 1400, 1220, 1081, 900 cm^{-1}; EIMS m/z (rel intens) 182 (M^+, 7 %), 147 (35), 149 (65), 91 (70), 75 (100), 28 (45)