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Stereocontrolled Synthesis of (*E,E,E*)-Chlorotrienes: Efficient Intermediates for the Construction of *all E* Conjugated Polyenes

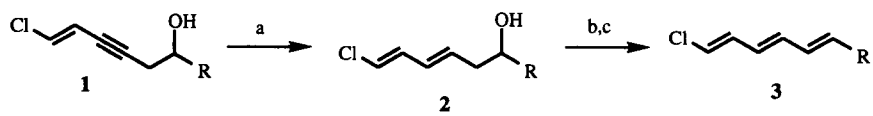
Benoit Crousse, Mouâd Alami* and Gérard Linstrumelle

Ecole Normale Supérieure, Département de Chimie associé au CNRS
24 rue Lhomond 75231 Paris Cedex 05, France

Abstract: Stereoselective reduction of conjugated homopropargylic alcohols **1** followed by an elimination reaction, allows an efficient approach to stereodefined (*E,E,E*)-chlorotrienes. The interest of these chlorotrienes was illustrated by a stereocontrolled synthesis of navenone B and *all E* conjugated polyenes (trienes, tetraenes and hexaenes). © 1997 Published by Elsevier Science Ltd.

Stereodefined halogenopolyenes are useful synthetic intermediates in organic synthesis, particularly for the stereospecific synthesis of polyunsaturated compounds.[1] Many methods are described for the preparation of halogenodienes.[2] However, they are few reports on the synthesis of halogenotrienes;[3,4] most of them, based on carbonyl homologation using Wittig type reagents, display little stereoselectivity.

As part of our studies on the synthesis of stereodefined polyenes,[1d,1h,5] we have recently reported a stereocontrolled synthesis of functionalized chlorotrienes *via* palladium mediated rearrangement of allylic acetates.[6] Herein we disclose a new and stereoselective approach to (*E,E,E*)-chlorotrienes **3** suitable for the rapid construction of conjugated polyene compounds. The key step of this approach is based on the stereoselective reduction of homopropargylic alcohols **1** into (*E*)-homoallylic alcohols **2** followed by an elimination reaction as outlined in scheme 1.



1 **2** **3**

Scheme 1: **(a)** Red-Al (1.3 equiv), Et_2O, -20° to 36°C, 2 to 5h; **(b)** MsCl (1.2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0° to rt; **(c)** DBU (1.5 equiv), CH_2Cl_2, 0° to rt.

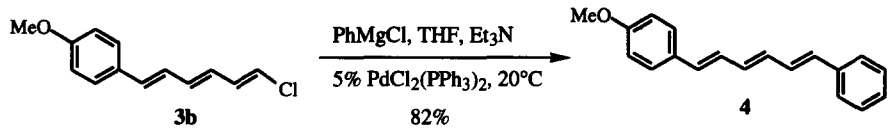
*Fax: (+33) 01 44 32 33 25

Table I: Synthesis of Various Homoallylic Alcohols **2** and Chlorotrienes **3**.

Entry	R	Isolated Yield of **2** (%)	Isolated Yield of **3** (%)	Product
1	C_6H_5	79	74	**a**
2	*p*-MeO-C_6H_4	62	72	**b**
3	*p*-*i*-Pr-C_6H_4	93	61	**c**
4	C_5H_{11}	82	45	**d**
5	H	90	-	**e**

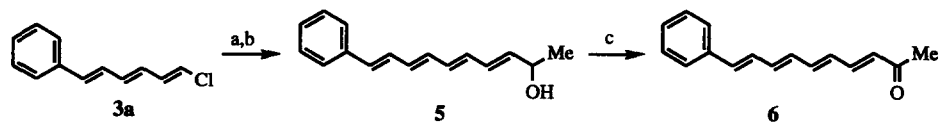
The required chloroenynes **1** were readily prepared by palladium-catalyzed coupling of (*E*)-1,2-dichloroethylene with 1-alkynes.[7] The stereoselective reduction of the homopropargylic alcohols **1** with Red-Al in Et_2O[8] led to the corresponding pure (*E,E*)-ω-chlorodienols **2** (62-93%, Table I). After treatment with methanesulfonyl chloride in CH_2Cl_2 followed by addition of DBU, the isomerically pure (*E,E,E*)-chlorotrienes **3**[9] were obtained in good overall yields (Table I).

These chlorotrienes would be of interest in organic synthesis since they are not photosensitive and they are more stable[10] than the corresponding iodides and bromides.[3d] In order to demonstrate the utility of these compounds for the stereospecific synthesis of polyene compounds, chlorotriene **3b** was subjected to coupling with a Grignard reagent in the presence of $PdCl_2(PPh_3)_2$ and Et_3N[11] in THF, thus providing an efficient route to isomerically pure (*E,E,E*)-diaryl hexatriene **4** in good yield (82%).



3b 82% **4**

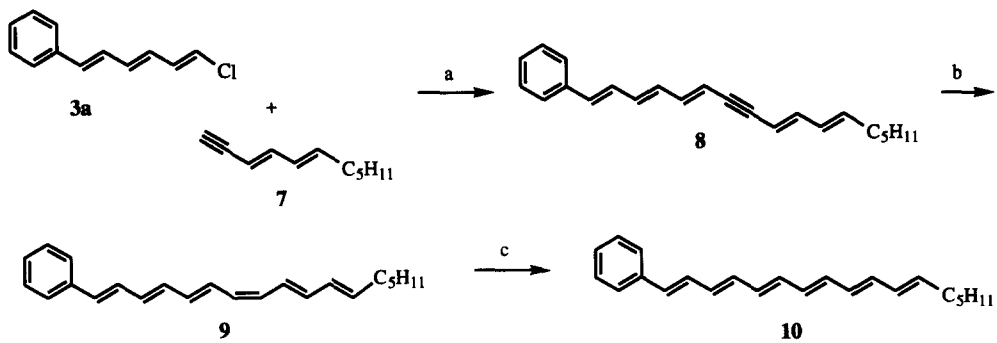
In a similar way, chlorotriene **3a** was also subjected to palladium-copper coupling[12] with 1-butyn-3-ol followed by selective reduction with Red-Al of the propargylic alcohol function to give the tetraene **5**[13] in 79% overall yield (Scheme 2). Subsequent oxydation of the allylic alcohol **5** with manganese oxide[14] in CH_2Cl_2 afforded in 80% yield navenone B **6**[15] which is an alarm pheromone of the mollusc *Navamax inermis*.[16]



3a **5** **6**

Scheme 2: (**a**) HC≡CCH(OH)Me, piperidine, 5% $PdCl_2(PhCN)_2$, 10% CuI, 20°C (95%); (**b**) Red-Al, Et_2O, -30° to 20°C (83%); (**c**) MnO_2, CH_2Cl_2, 20°C (80%).

Further demonstration of the utility of the chlorotrienes was the coupling of **3a** with dienyne **7**[7b] under Pd-Cu catalysis[12] followed by selective reduction of the triple bond. the pentaene **9** was not stable and give after isomerization at room temperature the pure hexaene **10** *all E*[17] as illustrated in scheme 3.



Scheme 3: (**a**) piperidine, 5% $PdCl_2(PhCN)_2$, 10% CuI, 20°C (60%); (**b**) Zn (Cu-Ag), MeOH-H_2O, 20°C; (**c**) 20°C (70% overall).

In conclusion, we have developed a novel and stereoselective approach to pure chlorotrienes **3** in a four step-sequence from available starting materials. These compounds are potentially interesting reagents since they are more stable than the corresponding bromides and iodides. Furthermore, they react easily and rapidly with organometallic reagents under appropriate conditions allowing access to conjugated polyenes.

Typical procedure for the preparation of (1E,3E,5E)-1-chloro-6-phenyl-1,3,5-hexatriene **3a**: To a stirred solution of chlorodiene **2a** (1.2 g, 5.80 mmol) and triethylamine (1.2 mL, 8.6 mmol) in CH_2Cl_2 (10 mL) was added at 0°C, methanesulfonyl chloride (0.55 mL, 6.96 mmol). After stirring at room temperature for 30 min, the mixture was hydrolyzed with a saturated aqueous solution of ammonium chloride and extracted with ether. The combined organic layers were washed with water until pH = 7, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product thus obtained was dissolved in CH_2Cl_2 (10 mL) and DBU (1.31 g, 8.6 mmol) was added at 0°C. The reaction mixture was stirred at room temperature overnight before to be hydrolyzed with a saturated aqueous solution of ammonium chloride and extracted with ether. The organic extract was dried over $MgSO_4$ and the solvent was removed *in vacuo*.Filtration throught silica gel (petroleum ether / CH_2Cl_2 10%) gave 800 mg (74%) of pure chlorotriene **3b**: ^{1}H-NMR (400 MHz): δ 7.44 (2H, d, J = 7.0Hz), 7.36 (2H, t, J = 7.0Hz), 7.27 (1H, t, J = 7.0Hz), 6.83 (1H, dd, J = 16.0 and 10.5Hz), 6.64 (1H, d, J = 16.0Hz), 6.58 (1H, dd, J = 13.0 and 10.5Hz), 6.43 (1H, dd, J = 15.0 and 10.5Hz), 6.31 (1H, dd, J = 15.0 and 10.5Hz), 6.28 (1H, d, J = 13.0Hz); ^{13}C NMR (100 MHz): δ 136.95, 133.75, 133.75 (for 3 C), 128.80, 128.55, 128.25, 127.75, 128.40, 128.40, 120.75; CIMS (rel int) 208 (30%), 191 (100%); UV: (CH_2Cl_2) λ = 322 nm (ε_{max} = 40000), λ = 337 nm (ε = 29500); m.p (*i*-Pr_2O): 99-101°C.

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15. **6**: ^{1}H-NMR (400 MHz): δ 7.46 (2H, d, J = 7.5Hz), 7.37 (2H, t, J = 7.4Hz), 7.31 (1H, d, J = 7.5Hz), 7.23 (1H dd, J = 15.0 and 11.0Hz), 6.91 (1H, dd, J = 15.0 and 10.4Hz), 6.74 (1H, dd, J = 14.0 and 11.0Hz), 6.72 (1H, d, J = 15.0Hz), 6.64 (1H, dd, J = 14.0 and 11.0Hz), 6.48 (1H, dd, J = 14.0 and 11.0Hz), 6.42 (1H, dd, J = 14.0 and 11.0Hz), 6.20 (1H, d, J = 15.5Hz), 2.32 (3H, s); ^{13}C NMR (100 MHz): δ 198.30, 143.20, 141.55, 137.70, 136.85, 135.30, 132.15, 130.50, 129.85, 128.70, 128.45, 128.15, 126.65, 27.35.
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17. **10**: ^{1}H-NMR (400 MHz): δ 7.45 (2H, d, J = 7.0Hz), 7.35 (2H, t, J = 7.0Hz), 7.25 (1H, d, J = 7.0Hz), 6.89 (1H, m), 6.59 (1H, d, J = 15.0Hz), 6.47 to 6.29 (8H, m), 6.14 (1H, dd, J = 15.0 and 10.0Hz), 5.88 (1H, dt, J = 15.0 and 7.0Hz), 2.25 (2H, q, J = 7.0Hz), 1.45 (2H, quint, J = 7.0Hz), 1.37 to 1.25 (4H, m), 0.92 (3H, t, J = 7.0Hz); ^{13}C NMR (100 MHz): δ 137.50, 136.30, 133.85, 133.75, 133.05, 132.65, 132.35, 130.80, 130.60, 129.30, 127.45, 128.65, 126.35, 32.95, 31.45, 29.00, 22.55, 14.05; CIMS (rel int) 305 (100%); UV: (CH_2Cl_2) λ = 381 nm (ε_{max} = 34700); m.p (CH_2Cl_2: petroleum ether): 173-175°C.

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