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SYNTHESIS OF FUNCTIONALIZED ISOPRENES INVOLVING A TERMINAL ALKOXY GROUP AND THEIR HIGHLY REGIOSELECTIVE DIELS-ALDER REACTION

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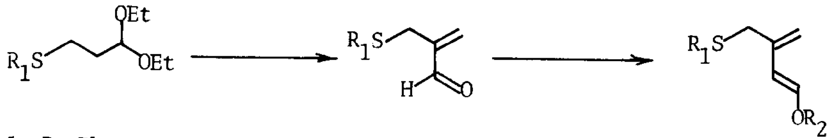
Summary: Functionalized isoprenes involving a terminal alkoxy group are newly synthesized, and a highly regioselective Diels-Alder reaction of these dienes with various unsymmetric dienophiles is described.

The Diels-Alder reaction of the isoprene unit with various dienophiles has proven to be one of the most useful synthetic methods for cyclic terpenoids.1) For this purpose, it is highly required that the dienes are suitably functionalized and the reaction proceeds regioselectively when unsymmetric dienophiles are employed. Nevertheless, few synthetically available dienes have been synthesized so far. Recently, Hosomi et al. have reported the highly regioselective Diels-Alder reaction of 2-trimethylsilylmethyl-1,3-butadiene in the presence of aluminum chloride catalyst.2)

In the course of our studies on functionalized isoprenes, we have encountered that 2-functionally-substituted-methyl-1,3-butadienes are not necessarily satisfactory with respect to regioselectivity.3) Since the introduction of an electron donating group at the terminal position of the diene uint seemed promising for improving the regioselectivity,1) we have turned our attention to synthesize functionalized isoprenes involving a terminal alkoxy group. And these compounds, in fact, were found to undergo almost completely regioselective Diels-Alder reaction with various unsymmetric dienophiles even without a Lewis acid catalyst.

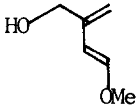
These dienes were conveniently prepared by the following sequence of reactions.



1a R_1=Ph
1b R_1=Et

2a R_1=Ph
2b R_1=Et

3a R_1=Ph, R_2=Me
3b R_1=Et, R_2=Me
3c R_1=Ph, R_2=CH_2CH_2OMe



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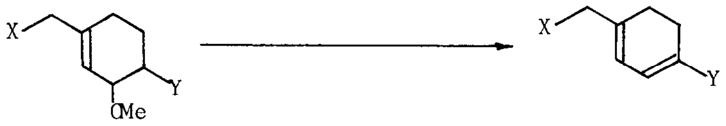
The sulfide 1[4] (60 mmol) was heated with a mixture of Me$_2$NH·HCl (120 mmol), 37 % formaline (120 mmol), and a catalytic amount of hydroquinone at 90 °C for 2 h under nitrogen.[5] The reaction mixture was extracted with ether and the organic layer was washed with water, dried (MgSO$_4$), and concentrated to give an oil which was purified by distillation to afford an exomethylenated aldehyde 2 in 53-65 % yields. The aldehyde 2 thus obtained was immediately reacted with a slight excess (1.1 eq) of phosphoranes (generated from $Ph_3\overset{+}{P}CH_2OCH_3$ Cl$^-$ [6] and $Ph_3\overset{+}{P}CH_2OCH_2CH_2OCH_3$ Cl$^-$ [7] and lithium isopropylcyclohexylamine at -30 °C for 2 h in THF) at -30 °C-r.t. for 2 h.[8] The reaction mixture was poured into ice-cold water and extracted with hexane. The organic layer was washed with water, dried (MgSO$_4$), and concentrated. The residue was distilled by Kugelrohr in vacuo to give the desired dienes 3 in 40-43 % yields. Oxidation of 3a (H_2O_2-MeOH, r.t. 12 h) and the Evans rearrangement[9] (excess of Et$_2$NH in MeOH, reflux, 12 h) gave the diene 4 in 50 % yield after silica gel column chromatography.

Although these dienes were obtained as a stereoisomeric mixture (1,2-trans:1,2-cis = 70:30), separation of stereoisomers was unnecessary for the Diels-Alder reaction because the cis isomer was recovered unchanged after the reaction.

Table shows the results of the Diels-Alder reaction of 3 and 4 with various unsymmetric dienophiles. GLC and NMR analyses of the products showed that the reaction proceeded with excellent regioselectivity. GLC of the adducts gave rise to two peaks and ^{13}C NMR spectra exhibited a pair of signals for each olefinic carbon. That these mixtures are stereoisomers was confirmed by ^{1}H NMR spectra which showed olefinic proton signals diagonostic of the endo/exo mixture.[10] The high regioselectivity was also indicated by the following chemical modification. Demethoxylation of the adducts 5 yielded the cyclohexadiene derivatives 6 exclusively. In these reactions, the meta isomer, if present, would never undergo similar demethoxylation.

The highly regioselective Diels-Alder adducts obtained in this study are useful for various cyclic terpenoid synthesis, details of which will be published in due course.



5 6

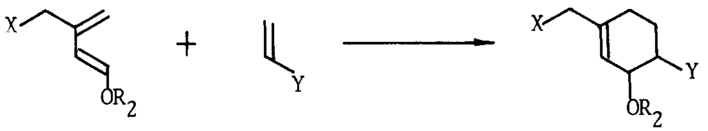
reaction conditions

a X=SPh, Y=COCH$_3$; 20% H$_2$SO$_4$-THF, r.t., 24 h

b X=OH, Y=COCH$_3$; 20% H$_2$SO$_4$-THF, r.t., 24 h

c X=OH, Y=CO$_2$CH$_3$; NaOCH$_3$-CH$_3$OH, r.t., 12 h

Table Diels-Alder reactions of dienes 3 and 4 with unsymmetric dienophiles



X=SPh, SEt, OH

Y=$COCH_3$, CO_2Me, CHO, CN

R_2=Me, CH_2CH_2OMe

Entry No	diene	dienophile	conditions[a)] temp(°C)	time(h)	yield of adduct[b)] (%)	endo:exo[c)]
1	3a	$CH_2=CHCOCH_3$	r.t.	24	73	81:19
2	3a	$CH_2=CHCO_2CH_3$	80	11	71	68:32
3	3a	$CH_2=CHCHO$	r.t.	24	59	74:26
4	3b	$CH_2=CHCOCH_3$	r.t.	24	70	81:19
5	3b	$CH_2=CHCO_2CH_3$	80	11	78	75:25
6	3c	$CH_2=CHCOCH_3$	r.t.	24	57	81:19
7	3c	$CH_2=CHCO_2CH_3$	80	24	54	63:37
8	3c	$CH_2=CHCHO$	r.t.	24	52	80:20
9	3c	$CH_2=CHCN$	80	24	59	63:37[d)]
10	4	$CH_2=CHCOCH_3$	r.t.	24	63	71:29
11	4	$CH_2=CHCO_2CH_3$	80	10	88	82:18

[a)] Benzene was employed as a solvent. Reaction conditions were not optimized.

[b)] Isolated yields after column chromatography on silica gel and calculated based on the trans isomer.

[c)] Determined with NMR spectra (see text).

[d)] Isolated ratio by column chromatography on silica gel (hexane/ether 3:1).

NMR spectra δ (CCl_4)

2a: 3.64 (s, 2H, CH_2S), 5.96 (s, 1H, C=CH), 6.23 (s, 1H, C=CH), 7.20 (m, 5H, SPh), and 9.48 (s, 1H, CHO).

2b: 1.25 (t, 3H, CH_3, J = 7 Hz), 2.45 (q, 2H, CH_2, J = 7 Hz), 3.27 (s, 2H, SCH_2C=C), 6.00 (s, 1H, C=CH), 6.31 (s, 1H, C=CH), and 9.50 (s, 1H, CHO).

3a: 3.57 (s, 3H, OCH_3), 3.64 (s, 2H, SCH_2), 4.70-5.10 (m, 2.3H, C=CH_2 and CH=CO (cis)), 5.38 (d, 0,7H, CH=CO, trans, J = 13 Hz), 5.85 (d, 0.3H, C=CHO, cis, J = 7 Hz), 6.65 (d, 0.7H, C=CHO, trans, J = 13 Hz), and 7.19 (m, 5H, SPh).

3b: 1.18 (t, 3H, CH_3, J = 7 Hz), 2.38 and 2.41 (q, 2H, CH_2, J = 7 Hz), 3.17 (s, 2H, SCH_2C=C), 3.55 and 3.65 (s, 3H, OCH_3), 4.60-4.90 (m, 2H, C=CH_2), 5.10-5.21 (m, 0.3H, CH=CO, cis), 5.35 (d, 0.7H, CH=CO, trans, J = 13 Hz), 5.86 (d, 0.3H, C=CHO, cis, J = 7 Hz), 6.70 (d, 0.7H, C=CHO, trans, J = 13 Hz).

3c: 3.34 (s, 3H, OCH_3), 3.40-4.05 (m, 4H, OCH_2CH_2O), 3.60 (s, 2H, SCH_2), 4.70-5.15 (m, 2.3H, C=CH_2 and CH=CO (cis)), 5.48 (d, 0.7H, CH=CO, trans, J = 13 Hz), 5.99 (d, 0.3H, C=CO, cis, J = 7 Hz), 6.65 (d, 0.7H, C=CHO, trans, J = 13 Hz), and 7.15 (m, 5H, SPh).

4: 3.45 and 3.68 (s, 3H, OCH_3), 4.08 (s, 2H, CH_2O), 4.70-5.00 (m, 2.3H, C=CH_2 and CH=CO (cis)), 5.35 (d, 0.7H, CH=CO, trans, J = 13 Hz), 5.79 (d, 0.3H, C=CHO, cis, J = 7 Hz), and 6.64 (d, 0.7H, C=CHO, trans, J = 13 Hz).

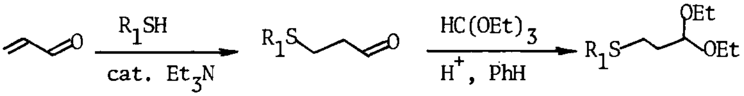
References and Notes

1) M. Petrzilka and J. I. Grayson, Synthesis, 1981, 753.

2) A. Hosomi, H. Iguchi, J. Sasaki, and H. Sakurai, Tetrahedron Lett., 23, 551 (1982).

3) T. Mandai, H. Yokoyama, T. Miki, H. Fukuda, H. Kobata, M. Kawada, and J. Otera, Chem. Lett., 1980, 1057.

4) The sulfide 1 was prepared as follows:



5) R. Menicagli and M. Luciawis, J. Chem. Res. (S), 1978, 262.

6) G. Wittig and M. Schlosser, Chem. Ber., 94, 1373 (1961).

7) $CH_3OCH_2CH_2OCH_2Cl \xrightarrow[PhH, reflux]{Ph_3P} Ph_3\overset{+}{P}CH_2OCH_2CH_2OCH_3\ Cl^-$

Cf: E. J. Corey, J. L. Gras, and P. Ulrich, Tetrahedron Lett., 1976, 809.

8) 1-Methoxy-3-methyl-1,3-butadiene has been prepared from methacrolein by the Wittig condensation.

Cf: T. R. Kelly, Tetrahedron Lett., 1978, 1387.

9) M. Kodama, K. Shimada, T. Takahashi, C. Kabuta, and S. Ito, Tetrahedron Lett., 22, 4271 (1981).

10) S. Danishefsky, T. Kitahara, C. F. Yan, and J. Morris, J. Am. Chem. Soc., 101, 6996 (1979).

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