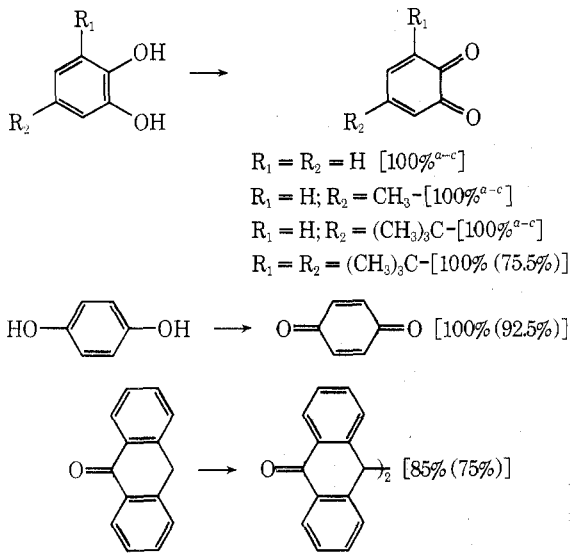
Scheme I



[a] Percentage obtained by nmr and ir analysis. [b] Isolated yields are in parenthesis, identical with authentic sample, one spot on tlc, no depression in mixture melting point. [c] Sterically unhindered *o*-quinones are unstable in concentrated solution, undergoing both polymerization and Diels–Alder dimerization. The degradation (at 35°) could be followed by nmr and a black polymer was rapidly formed in concentrated solution. However, dilute solutions of the beautiful red material could be kept for several days with no extensive degradation at 5–10°. It is best to use these unhindered *o*-quinones relatively soon after synthesis.

Corey and Kim[17] have noted that, in the NCS–DMS oxidations, TEA was the base of choice that gave the best yields.

A typical experimental procedure is given below.

To a stirred and cooled (−25°) solution of 400 mg (3 mmol) of *N*-chlorosuccinimide in 15 ml of methylene chloride was added 445 mg (2 mmol) of 3,5-di-*tert*-butylcatechol. After a 10-min interval, 0.3 ml of TEA was added dropwise. Stirring at −25° was continued for 10 min. The mixture was filtered and the filtrate evaporated. The dark red residue was dissolved in hot hexane, filtered, evaporated down to a few milliliters (until crystallization was apparent), and allowed to cool. The crystalline product (333 mg, 75.5%) thus obtained was identical in all respects with authentic *o*-quinone (Aldrich Chemical Co.).

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(19) J. P. Marino and A. Schwartz [*Chem. Commun.*, 812 (1974)] have reported a similar oxidation using NCS–DMS–TEA to form *o*-quinones and *p*-quinones in high yields. Interestingly these authors comment on the necessity for TEA but did not comment on its activating and accelerating effect. They also confirmed our control experiments. In the initial part of this work we performed the reaction with and without DMS present and found that there was no significant difference in yield or product distribution between the two reactions except in the coupling of anthrone, where a slightly purer product was obtained. Thus we feel that, when DMS is present, it may participate in the reaction but in many reactions it may not be necessary.

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γ-Alkylation of 2-Butynoic Acid. A Route to Controlled Prenol Homologation

Summary: The novel γ-alkylation of 2-butynoic acid allows a facile synthesis of *Z* trisubstituted olefins, and of *Z* isoprenoid systems in particular.

Sir: The elaboration of polyisoprenoid compounds has recently been the focus of numerous studies owing to the crucial role of polyisoprenoids in many biological systems. Insect juvenile hormones[1] and insect sex attractants[2] are isoprenoid in nature. The long-chain polyprenols exemplified by bactiprenol and dolichol participate in polysaccharide and glycoprotein synthesis in both prokaryotic and eukaryotic systems.[3]

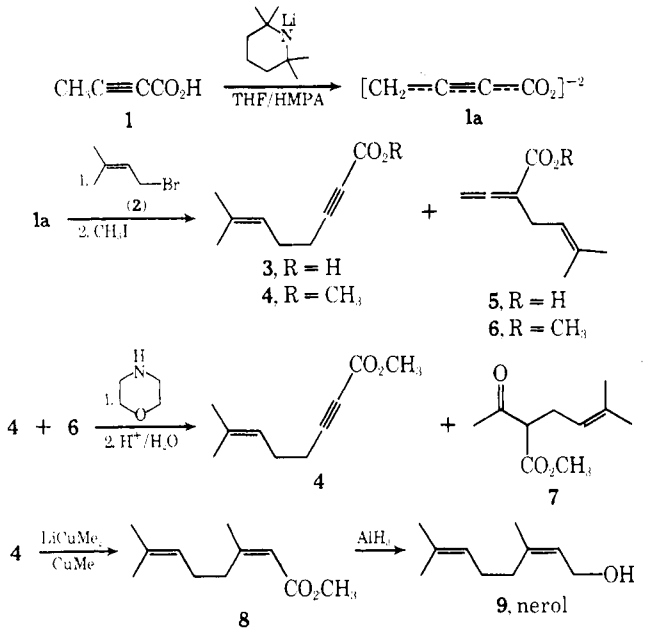
The synthesis of *E* polyisoprenoid systems has been well established, and new preparations are still being described.[4] There are, however, very few preparations of *Z* trisubstituted olefins.[2,5,6] Recently Casey and Marten[5] reported a technique for isoprenoid synthesis involving γ-alkylation of methyl acetoacetate[5a] and stereospecific olefin synthesis using enol acetates and lithium dimethyl cuprate.[5b] We wish to report an alternative route to (*Z*)-isoprenols permitting a greater degree of stereoselectivity in the olefin synthesis. The technique involves the novel γ-alkylation of 2-butynoic acid (**1**) with 1-bromo-3-methyl-2-butene (**2**), esterification of the resulting 7-methyloct-6-en-2-ynoic acid (**3**), and treatment of this methyl ester (**4**) with lithium dimethyl cuprate[7] to give the desired methyl (*Z*)-3,7-dimethylocta-2,6-dienoate (**8**). This ester is reduced to nerol [(*Z*)-3,7-dimethylocta-2,6-dien-1-ol, **9**] with AlH_3.[8]

Alkylation of α,β-unsaturated esters and aldehydes always leads exclusively or preponderantly to α substituanion of methyl 2-butynoate primarily in the α position, giving the allene, methyl 2,3-butadienoate, as the major product. Katzenellenbogen and Crumrine[10] were able to partially γ-alkylate the copper(I) dienolate of ethyl (*E*)-3-methyl-2-hexenoate with allyl bromide, but use of 3,3-disubstituted allyl bromides gave only α-alkylation.

The development of α-alkylation of carboxylic acids *via* their dianions[11] suggested to us that the negatively charged dianion of 2-butynoic acid might be delocalized in such a way that the alkylation process would favor γ-alkylation.

We found that treatment of 2-butynoic acid (**1**) with slightly more than a 2 molar ratio of lithium 2,2,6,6-tetramethylpiperidide[12] yields a dianion (**1a**) which, when alkylated with 1-bromo-3-methyl-2-butene (**2**), yields a mix-

Scheme I



ture of the salts of two acids, **3** and **5**. These acid salts are methylated with MeI in DMF to form esters **4** and **6**. The ratio of ene–yne ester (γ-alkylation, **4**) to ene–allene ester (α-alkylation, **6**) is 2.2:1.[13] The yield of the desired product(**4**) is 53–59% by gc. The dianion (**1a**) formation is carried out by rapidly adding a 10% solution of **1** in dry HMPA to a solution of lithium 2,2,6,6-tetramethylpiperidide (2.1 molar ratio to **1**) in dry THF (7 volumes of THF/volume of HMPA) which is at −100°. The addition should not be so rapid as to elevate the reaction temperature above −60°. The reaction mixture is then cooled to −90°, and the bromide (**2**) (equimolar with butynoic acid) is added rapidly. The cold bath is then allowed to warm to −70°, and the reaction is maintained at this temperature for 1.5 hr, at which time it is quenched with excess MeOH.

The variation of the HMPA:THF ratio in this reaction was limited by the relatively high freezing point of HMPA. Use of a 1:1 HMPA:THF ratio limited the lowest temperature to *ca.* −60°, owing to crystallization of HMPA from the solution. The yield of desired product (**4**) was small, and the ratio of **4**:**6** was essentially the same as for the run using 7:1 THF:HMPA. The use of much smaller amounts of HMPA caused a reduction in the ratio of **4**:**6**. At 50:1 THF:HMPA, the ratio of **4**:**6** was ~1:1.

Increasing the temperature in the dianion formation step (at 7:1 THF:HMPA) led to a lower yield of product, probably due to condensations between butynoic anions and unionized acid. Decreasing the dianion formation temperature below −100° caused problems of inhomogeneity due to crystallization of HMPA and/or dilithium butynoate from the reaction mixture.

After methylation, the resulting desired γ-alkylation product **4** may be separated from the α-alkylation product **6** by treatment with morpholine[14] in Et_2O at 20° for 1 hr, followed by acid work-up. Separation of **4** from **7** is then possible by means of silica gel column chromatography using EtOAc–Skelly B eluents. The ene–yne ester **4** is isolated in 36–40% yield, calculated from **1**.

Treatment of **4** (5 g, 30.4 mmol) with a mixture of $LiCuMe_2$ (8 molar ratio to **4**) and CuMe (2 molar ratio to **4**) at −70° in THF for 6 hr was followed by a typical work-up,[15] giving **8** (4.1 g, 22.4 mmol, 74% yield) as a mixture with a *Z*:*E* ratio of 54:1 (isomeric purity of 98.2%) by gc. This compares with a *Z*:*E* ratio of 7.1:1 previously reported for the same compound,[5b] achieved by a different route. The two isomers can be differentiated by their nmr spectra (60 MHz in $CDCl_3$, TMS as internal standard): *Z* isomer, δ 1.90, assigned to the 3-methyl group; *E* isomer, δ 2.18, also assigned to the 3-methyl group.

A mixture of $LiCuMe_2$ and CuMe was used to ensure that no MeLi was present in the reaction mixture, since Corey and Katzenellenbogen[7] have suggested that the presence of MeLi leads to increased amounts of *E* isomer. When only CuMe was used to effect the addition across the acetylenic bond, the reaction was very slow, leaving large amounts of starting material after 6 hr at −70° in THF.

In a separate attempt to synthesize the *E* isomer of **8**, **4** was treated with a mixture of $CuLiMe_2$ (3 molar ratio to **4**) and MeLi (0.5 molar ratio to **4**) in THF. The reaction was started at 0° and allowed to warm to 22° over 4 hr. The resulting product ratio (gc) was 1:1.6 *Z*:*E*, with no starting material remaining. This ratio of products was so disappointing that this reaction to synthesize the *E* isomer of **8** was not pursued any further.

Treatment of **8** with AlH_3[8] yields the desired product, nerol (**9**). Comparison of the nmr spectrum [as above, with 120 mg of $Eu(FOD)_3$ added] of synthetic nerol with the spectrum of the purified commercially available material shows the two to be identical. The synthetic material also has the same retention time (gc) as the natural material, and a mixture of the two are eluted as one peak.

The isomerization technique of Cardillo, *et al.*,[4] applied at the neroate stage (**8**) potentially allows homologation of isoprenoid units with complete stereochemical control at each double bond.

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