mixture was stirred for 1 h, quenched with aqueous NH_4Cl solution, allowed to warm to room temperature, and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under vacuum to give 0.289 g of residue which could be further purified by reversed-phase HPLC (Whatman Partisil M9 10/50 ODS-2, CH_3CN, 4.0 mL/min). The crude residue was usually directly benzoylated as described in the next section: ^1H NMR ($CDCl_3$) δ 0.06 (6 H, $(CH_3)_2Si$, s), 0.88 (9 H, $(CH_3)_3CSi$, s), 0.98 (6 H, $C_{16,17}$-$2CH_3$, s), 1.68 (C_{18}-CH_3, s), 3.67 (2 H, H_{15}, m), 5.40 (1 H, H_{11}, s), 5.45 (1 H, H_8, d, $J \sim 16.6$ Hz), 6.54 (1 H, H_7, d, $J \sim 16.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 140.8, 138.9, 137.6, 136.9, 131.1, 111.8, 88.8, 84.7, 63.1, 60.9, 39.5, 37.8, 34.7, 33.9, 33.0, 32.6, 29.8, 28.6, 27.4, 26.3, 26.0, 21.5, 19.0, 18.4, -5.5; IR (neat film) ν 3430 (OH, br), 3010 (C=CH), 2230 (C≡C, w), 1470, 1460, 1380, 1360, 1255, 1000, 950, 830 cm^{-1}; exact mass, m/z 438.3321 (calcd for $C_{29}H_{48}O_2Si - H_2O$, 438.3319); MS, m/z 439 (12), 438 (33, M - H_2O), 307 (12), 306 (11), 293 (24), 291 (37), 237 (17), 223 (13), 159 (12), 145 (21), 133 (12), 131 (12), 129 (10), 105 (16) 91 (20), 89 (17), 81 (11), 75 (base) 73 (69), 69 (18), 59 (11), 55 (16); ≳10% plus key peaks.

(7*E*,12*Z*)-12,20-Tetramethylene-9,10-didehydro-11,14-dihydro-9-demethyl-11-(benzoyloxy)retinyl *tert*-Butyldimethylsilyl Ether (11a). A solution of benzoyl chloride (0.095 g, 0.67 mmol) in pyridine (0.24 mL) was added to the crude alcohol **11b** (0.289 g) described above. (Dimethylamino)pyridine (0.010 g) was added, and the reaction mxiture was stirred for 3 h and then extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated under vacuum. The residual product was subjected to Chromatotron purification (silica gel, 90:10:2, hexanes–ether–pyridine) to afford 0.268 g of the benzoate **11a** in a yield of 71% (based on the aldehyde **12**): ^1H NMR, ($CDCl_3$) δ 0.01 (6 H, $(CH_3)_2Si$, s), 0.81 (9 H, $(CH_3)_3CSi$, s), 0.93 (6 H, $C_{16,17}$-$2CH_3$, s), 1.63 (3 H, C_{18}-CH_3, s), 3.61 (2 H, H_{15}, m), 5.40 (1 H, H_8, d, $J \sim 16.3$ Hz), 6.51 (1 H, H_7, d, $J \sim 16.3$ Hz), 6.58 (1 H, H_{11}, br s), 7.3–7.5 (3H, *m*- and *p*-phenyl, m), 7.99 (2 H, *o*-phenyl, d, $J \sim 7.3$ Hz); IR, (neat film) ν 2930 (s) 2860 (s), 2205 (C≡C, w), 1725 (CO, s), 1605, 1590, 1480, 1460, 1260, 1180 cm^{-1}; exact mass, m/z 438.3313 (calcd for $C_{36}H_{52}O_3Si - C_6H_5COOH$, 438.3319); MS, m/z 439 (8), 438 (21, M - C_6H_5COOH), 307 (10), 306 (22), 304 (6), 293 (13), 292 (6), 291 (26), 237 (9), 181 (6), 179 (8), 159 (6), 147 (7), 145 (15), 143 (6), 133 (8), 122 (19), 77 (12), 75 (base), 73 (11), 56 (7), 55 (7), 44 (11), 43 (6), 41 (21); >5% plus key peaks.

(7*E*)-12,20-Tetramethylene-10,14-*retro*-retinyl *tert*-Butyldimethylsilyl Ether (5a). A solution of CH_3MgBr (2.85 M in ether, 0.46 mL, 1.31 mmol) was added to a well-stirred mixture of LiBr (0.115 g, 1.33 mmol) and CuI (0.253 g, 1.33 mmol) in THF (5.50 mL) at 0 °C, and the solution was stirred for 15 min. The propargylic benzoate **11a** (0.124 g, 0.22 mmol) in THF (1.30 mL) was added dropwise and the reaction mixture stirred for 1 h at 0 °C, quenched with aqueous NH_4Cl, and extracted with ether. The organic layer was washed with aqueous $NaHCO_3$ solution and brine and then dried over $MgSO_4$ and evaporated under vacuum. The residual product was subjected to Chromatotron purification (silica gel, 100:2:2, hexane–ether–pyridine) to give 0.075 g (76%) of the product which had already undergone a considerable amount of rearrangement. This product mixture was normally carried through the next step without further separation.

12,20-Tetramethyleneretinols 1, 2, 3, and 4. A solution of *n*-Bu_4NF (1.0 M in THF, 1.95 mL, 1.95 mmol) was added to partially rearranged vinylallene silyl ether **5a** (0.288 g, 0.65 mmol) from the preceding experiment, and the mixture was stirred under an atmosphere of nitrogen for 2 h. The mixture was then quenched with saturated brine and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ and saturated brine and then dried over anhydrous $MgSO_4$. After concentration under vacuum, the residual product was subjected to Chromatotron purification (silica gel, 2% pyridine/2:2:1 hexane–ether–dichloromethane). Examination of the product at this stage by ^1H NMR and IR indicated that the vinylallene had undergone complete rearrangement to the retinols. The mixture was subjected to preparation HPLC (Whatman Partisil M9 10/50; 15% ethyl acetate/Skellysolve B; 4.0 mL/min) to give a mixture of 11-*cis*-1 and 11-*cis*,13-*cis*-3; 9-*cis*,11-*cis*,13-*cis*-4; and 9-*cis*,11-*cis*-2, respectively. The mixture of 11-*cis*-1 and 11-*cis*-13-*cis*-3, the former eluting first, was separated by HPLC recycling under the same conditions. The four 12,20-tetramethyleneretinols were obtained in the following yields (a 50% mass balance after separation): 11-*cis*-1 (10 mg, 4.5%), 11-*cis*,13-*cis*-3 (26 mg, 12%), 9-*cis*,11-*cis*,13-*cis*-4 (60 mg, 27%), and 9-*cis*,11-*cis*-2 (14 mg, 6.3%).

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Registry No. 1, 85236-05-1; 2, 85236-07-3; 3, 85236-09-5; 4, 85236-11-9; 5a, 85236-03-9; 7, 85236-17-5; 11a, 96617-88-8; 11b, 96617-90-2; 12, 96617-89-9; 13, 73395-75-2.

α-^{14}C and ^{34}S Isotope Effects in E2 Reactions of (2-Phenylethyl)dimethylsulfonium Ion[1]

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Leaving-group isotope effects have been used by us and by others to probe transition-state structure in bimolecular elimination reactions.[2] The nitrogen isotope effect ($^{14}N/^{15}N$) for the reaction of (2-phenylethyl)trimethylammonium ion with hydroxide ion in Me_2SO–H_2O mixtures at 60 °C changes little as the composition of the solvent changes, ranging from 1.0087 in water to 1.0066 in 57% Me_2SO.[3] The effect essentially levels off above 30% Me_2SO, remaining between 1.0066 and 1.0072 with standard deviations of 0.00001–0.0006. With these results in mind, it is not surprising that the α-^{14}C isotope effect is similarly invariant between 30 and 50% Me_2SO at 1.0269 ± 0.0023.[4] The nitrogen isotope effects correspond to relatively little carbon–nitrogen bond cleavage in the transition state, only 15–20%.[3]

Sulfur isotope effects ($^{32}S/^{34}S$) in E2 reactions of sulfonium salts with hydroxide ion in Me_2SO–H_2O mixtures at 40 °C have been reported to decrease rather precipitously with increasing Me_2SO concentration, from 1.0074 in water to 1.0011 in 20% Me_2SO.[5] In the present paper we report an extension and (in part) correction of these results, as well as ^{14}C isotope effects.

The results are presented in Table I. The earlier result of 1.0011 in 20% Me_2SO[5] is evidently too low, as is probably the result of 1.0038 in 10% Me_2SO,[5] although it was not rechecked. We have no sure reason for the discrepancy, but we point out that the isotopic composition of the original sulfonium salt was determined directly on sulfur dioxide obtained by combustion in the present work, rather than on methyl sulfide obtained by "100%" reaction with base as in the earlier work.[5] Incomplete reaction, or failure to collect all of the "100%" sample of methyl sulfide should lead to a low apparent isotope effect. We also note that

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0022-3263/85/1950-2392$01.50/0

Table I. ^{34}S and α-^{14}C Isotope Effects in E2 Reactions of (2-Phenylethyl)dimethylsulfonium Ion with Hydroxide Ion in Me_2SO-H_2O and with Ethoxide Ion in Ethanol

base/sol[a]	temp, °C	k_{32}/k_{34}[b]	k_{12}/k_{14}[c]
OH^-/20% Me_2SO	40	1.0064 ± 0.0003	
OH^-/30% Me_2SO	40	1.0043 ± 0.0003	
	50		1.0268 ± 0.0029
OH^-/40% Me_2SO	50		1.0262 ± 0.0007
OH^-/43% Me_2SO	40	1.0025 ± 0.0007	
OH^-/50% Me_2SO	50		1.0203 ± 0.0010
EtO^-/EtOH	50		1.0288 ± 0.0019
OH^-/H_2O	40	1.0074[d]	

[a] Solvent compositions expressed in mol %. [b] Each is average of two (20% and 43% Me_2SO) or three (30% Me_2SO) runs with standard deviation of mean. [c] Each is average of three runs at fractions of reaction, F, of 0.51–0.79. Deviation is standard deviation of the mean. [d] Reference 5.

there was substantial scatter (1.0002–1.0028) in the results contributing to the 1.0011 value in 20% Me_2SO, where 5% reaction took only 9 min.[5] The present pattern, then, is that k_{32}/k_{34} remains near 1.0070 to 20% Me_2SO but decreases to 1.0025 in 43% Me_2SO. Not only is there a definite decrease in k_{32}/k_{34}, but the values correspond to greater carbon–sulfur bond weakening in the transition state (60–75% in H_2O to 20–25% in 43% Me_2SO[3]) than was the case for carbon–nitrogen bond weakening with the corresponding ammonium salt (see above).

The α-^{14}C effects show little or none of this change. They are almost invariant, except for the possibly smaller value in 50% than in 30 or 40% Me_2SO, and the average value in the three solvent mixtures (1.0244 ± 0.0036) does not differ significantly from the corresponding average for the ammonium salt (1.0269 ± 0.0023). The result with ethoxide/ethanol again hardly differs from those in the mixed solvents.

Thus the α-carbon isotope effects seem to remain between 1.020 and 1.029 regardless of solvent, leaving group, or the extent of weakening of the bond to the leaving group in the transition state. The probable explanation of this result is that a carbon–carbon double bond is forming as the carbon–leaving group bond is breaking. Thus the total strength of bonding to the α-carbon does not change much as the bond to the leaving group is progressively weakened. Model calculations bear out this analysis, giving α-^{13}C isotope effects which remain almost constant from a reactant-like to a product-like model when all bond changes are concerted.[6] The model does predict larger α-^{14}C isotope effects with NMe_3 than with SMe_2 as leaving group for any given extent of carbon–leaving group cleavage in the transition state. While this difference is not observed in the present results, it must be remembered that the carbon–sulfur bond is more weakened in the transition state than the carbon–nitrogen bond where direct comparisons can be made. This may compensate for the intrinsically larger effect with the quaternary ammonium salt. It is also worth noting that the model predicts a not insignificant contribution of tunneling to k_{12}/k_{14} when the β-hydrogen is approximately symmetrically located between β-carbon and base in the transition state.[6] The relative contributions of this factor to the sulfonium and ammonium salt reactions constitute another uncertainty in the interpretation of the results.

Experimental Section

Solvents. Distilled water was refluxed over potassium permanganate for 2 h and distilled. Absolute ethanol was refluxed with magnesium turnings for at least 8 h and distilled. Dimethyl sulfoxide was stirred over calcium hydride for 2 days and distilled at reduced pressure. The first 10% of distillate from each solvent was discarded. Mixtures of water and Me_2SO were prepared by mixing weighed amounts calculated to give the desired mole percent. All compositions are in mole percent whether explicitly stated or not.

(2-Phenylethyl)dimethylsulfonium bromide was prepared from methyl 2-phenylethyl sulfide[7] (0.125 mol) and methyl bromide (0.125 mol) in 200 mL of absolute ethanol containing a little ether. The solution was prepared in an ice–salt bath and left standing for 24 h. The product was removed by filtration and recrystallized from absolute ethanol, followed by drying in vacuo at 76 °C to give 85% of pure material, mp 135–135.5 °C (lit.[8] mp 135.5 °C).

Sulfur isotope effects were determined by the procedure of Hargreaves, Katz, and Saunders.[9] For the more rapid reactions, the reaction was stopped at the desired extent of completion by using an insufficiency of base. Both the original sulfonium salt and the methyl sulfide samples were measured as sulfur dioxide in the same dual-collector mass spectrometer used before.[9] A few samples were measured by repeated scanning of m/e 64 and 66, with no apparent difference in results.

Phenylacetonitrile-*1*-^{14}C was obtained in 91% yield by refluxing benzyl bromide (0.35 mol), sodium cyanide-^{14}C (0.36 mol, 1 mCi), water (26 mL), methylene chloride (26 mL), and tetrabutylammonium bromide (0.01 mol) for 4 h. Unlabeled sodium cyanide (0.64 mol) was added and refluxing continued for another 4 h. Water was added, and the extracts were washed with water and dried over calcium chloride. After removal of the ether the product was distilled from phosphorus pentoxide; bp 86–87 °C (3 mm) (lit.[10] bp 115–120 °C (10 mm)); 91% yield.

Phenylacetic-α-^{14}C acid was prepared in 96% yield by acid hydrolysis of phenylacetonitrile-*1*-^{14}C according to the procedure of Adams and Thal.[11] The product had a melting point of 75–77 °C (lit.[11] mp 76–76.5 °C).

2-Phenylethanol-*1*-^{14}C was obtained in 94% yield by reducing phenylacetic-α-^{14}C acid (0.07 mol) with lithium aluminum hydride (0.1 mol) by the procedure of Amundsen and Nelson.[12] The product had a boiling point of 84 °C (13 mm) (lit.[7] 110 °C (20 mm)).

2-Phenylethyl-*1*-^{14}C *p*-toluenesulfonate was obtained in 83% yield from 2-phenylethanol-*1*-^{14}C by the procedure of Tipson.[13] The product had a melting point of 37.5–38.0 °C (lit.[7] mp 37.4–38.0 °C).

Methyl 2-phenylethyl-*1*-^{14}C sulfide was prepared in 92% yield by the procedure of Saunders and Edison.[7] The product had a boiling point of 87 °C (3 mm) (lit.[7] bp 121 °C (75 mm)).

(2-Phenylethyl-*1*-^{14}C)dimethylsulfonium bromide was prepared in 91% yield by treating methyl 2-phenylethyl-*1*-^{14}C sulfide (0.13 mol) with methyl bromide (30 mL) in 15 mL of ether and 30 mL of nitromethane. The procedure was the same as for the unlabeled material (above) except for solvent. The crude product was recrystallized from ethanol–ether to constant activity, mp 135.5–136 °C (lit.[8] 135.5 °C), molar activity 2.7142 mCi mol^{-1}.

Carbon isotope effects were measured for reaction with sodium ethoxide in ethanol and sodium hydroxide in 30, 40, and 50 mol % Me_2SO in water. The procedure followed was essentially that of Tao and Saunders.[4] The isotope effects were calculated from[14]

$$\frac{k_{12}}{k_{14}} = \frac{\log (1 - F)}{\log [(1 - F)R/R_0]}$$

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where F is the fraction of reaction (0.51–0.79 in the present experiments), R is the molar activity of recovered, and R_0 is the molar activity of the original reactant.

Registry No. ^{14}C, 14762-75-5; ^{34}S, 13965-97-4; (2-phenylethyl)dimethylsulfonium ion, 16315-48-3.

Proton-Transfer Steps in Steglich Esterification: A Very Practical New Method for Macrolactonization

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The development of synthetic methodology for the preparation of large ring lactones from the corresponding ω-hydroxy acids has, perhaps more than any other single development of recent years, dramatically impacted the field of natural products total synthesis. Practitioners of this art may now attack complex macrolide antibiotics secure in the knowledge that a variety of methods such as those due to Corey,[1] Mukaiyama,[2] Masamune,[3] and Mitsunobu[4] are available for formation of the large ring as the penultimate step in the synthesis and thus focus their creative efforts on the stereochemical challenges associated with such materials. In fact, it is probably not overstating the impact of macrolactonization methodology to trace the current explosion of methodology for "acyclic stereochemical control" to the availability of reliable macrolactonization procedures.

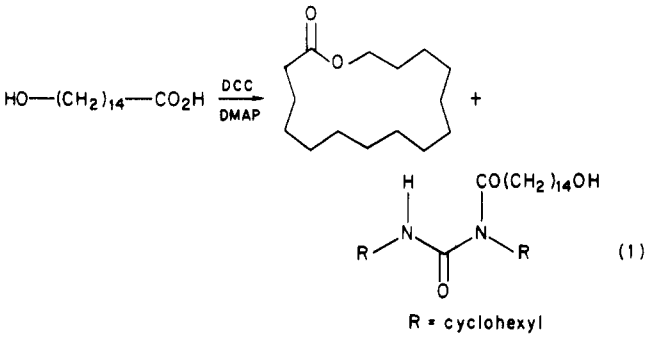
Despite the impressive advances in this area, some problems still remain, and our investigations on the macrocyclic bis-lactone colletodiol[5] have encouraged us not only to closely examine the available literature in this area but also to consider the characteristics of an "idealized" lactonization procedure. For example, in situ generation of an active ester is preferable to the formation of a discrete intermediate which is then subjected to macrolactonization conditions.[6] Moreover, activation of the carboxyl function should be accomplished in such a way as to allow for the regeneration of the active ester if the intermediate is destroyed by adventitious moisture. Finally, since these reactions are generally performed on rather small scale, reagents should be usable in excess without complicating conventional (e.g., TLC) chromatographic monitoring or product isolation.[7]

Consideration of these and other criteria has led us to examine Steglich[8] esterification, a very successful method for bimolecular esterification even with tertiary alcohols, as a method for macrolactonization. In this context it should be explicitly noted that the only chromatographically mobile (in common solvent systems) component derived from the reagents employed is dicyclohexylcarbodiimide (DCC), which can be converted, prior to isolation, to a urea which is generally easily removed by conventional techniques involving precipitation and chromatography.

Unfortunately, in our hands, all attempts at macrolactonization using this procedure, including those with excess reagents and very slow (syringe pump) addition of hydroxy acid, fail. For example, the VPC yield of the hexadecanolide from 15-hydroxypentadecanoic acid is only 4%, and the major isolable product is *N*-acylurea. (eq 1).

Table I. Isolated Yields of Lactones from ω-Hydroxy Acids

acid	lactone ring size	lactone yield, %	diolide yield, %
$HO(CH_2)_{11}CO_2H$	13	32	32
$HO(CH_2)_{12}CO_2H$	14	77	11
$HO(CH_2)_{14}CO_2H$	16	95	trace
$HO(CH_2)_{15}CO_2H$	17	96	



These results prompted us to critically examine the accepted mechanism for such esterifications, *including* proton transfer steps, with the conclusion that the failure might conceivably arise from low effective concentrations of alcohol and acid (both proton sources) under conditions appropriate for macrolactonization.[9] Therefore this approach to macrolactonization was reexamined in the presence of additives (specifically various amine hydrochlorides) to mediate such proton-transfer steps. Best results were obtained in media where such salts were totally soluble, and the use of DMAP·HCl as the amine hydrochloride proved most efficient and convenient. The optimal protocol is detailed below (vide infra), however, *for the present it is sufficient to note the isolated yield of crystalline hexadecanolide using this simple variation is 95%.*

Bimolecular esterification experiments verify the crucial role of such proton-transfer agents in preserving "active ester" species under conditions of high dilution. For example, exposure of cinnamic acid to DCC and 4-(di-

† Fellow of the Alfred P. Sloan Foundation, 1981–1985.

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