and steam distillation. No norcamphor was detected in organic extracts of the steam distillate. Method B gave a yield of 50% of **17** in the same ratio.

1-Butyl-2-methylcyclohexylamine (8). When **8** was subjected to the reaction conditions of method A, the solution remained homogeneous due to the greatly increased solubility of the *p*-nitrobenzenesulfonate salt, and the salt was not retained on the silica gel in the filtration step. The only identifiable product was the starting amine **8** (1.48 equiv out of 2 equiv). Method B gave the same result.

1-Butyl-2-methylcyclopentylamine (9). Use of method A failed to yield any product except the starting amine **9**. As seen for **8**, the reaction remained homogeneous, and the salt was not retained of the silica gel filter.

1-Butyl-3-methylcyclohexylamine (10). Use of method A failed to yield any product except starting amine **10**. As seen for **8**, the reaction remained homogeneous, and the salt was not retained on the silica gel filter.

Rearrangement of *N*-(1-Benzylcyclohexyl)hydroxylamine (22). A solution of **22** (500 mg, 2.44 mmol) and triethylamine (530 mg, 5.24 mmo) in dry THF (15 mL) was cooled to −30 °C, and a solution of *p*-nitrobenzenesulfonyl chloride (540 mg, 2.44 mmol) in dry THF (10 mL) was added dropwise over 10 min. The solution was stirred at −30 °C for 1 h and allowed to warm to room temperature. After 4 h at room temperature, during which time a heavy precipitate formed, the mixture was filtered, and the filtrate was stirred with 10% sodium hydroxide for 30 min. The layers were separated, the basic layer was extracted with dichloromethane (3 × 30 mL), and the combined organic fraction was dried ($MgSO_4$) and evaporated. The resulting pale yellow oil was dried in vacuo to give **13** (390 mg, 85%).

Rearrangement of *N*-(1-Butylcyclohexyl)hydroxylamine (23). By the procedure described above, **23** (340 mg, 1.96 mmol) was reacted with *p*-nitrobenzenesulfonyl chloride (430 mg, 1.96 mmol) and triethylamine (450 mg, 4.4 mmol) to give **12** (170 mg, 53%). Also present was **2** (10%). The same conversion could be accomplished in 44% by first making the potassium salt of **23** with KH in THF at −78 °C and then adding the sulfonyl chloride solution. After reaction for 3 h, the solution was warmed to room temperature and the above procedure continued.

Rearrangement of *N*-(1-Butyl-2-methylcyclohexyl)-hydroxylamine (24). By the procedure described above, **24** (350 mg, 1.9 mmol) was reacted with *p*-nitrobenzenesulfonyl chloride (420 mg, 1.9 mmol) and triethylamine (400 mg, 4 mmol) to give a mixture of ring-expanded imines **26–29** (78%), of which the major component was **26** (57%). Imine **26** was isolated by preparative VPC (column D) as a clear oil: ^1H NMR δ 0.90 (t, 3 H, butyl CH_3), 1.03–1.83 (m, 10 H, methylene H), 2.05 (d, 3 H, CH_3), 2.26 (m, 2 H, allylic H), 2.46 (m, 2 H, allylic H), 3.22 (m, 1 H, CHN=); IR (cm^{-1}) 2920, 2850, 1710 (weak), 1658, 1442; MS *m/e* 167 (P), 152 (P − 15), 138, 124, 110 (P − 57), 95. As seen in the IR, a small amount of ring opening was observed in the imine. Therefore the imine was reduced with $NaBH_4$[27] to 2-butyl-7-methyl-1-azacycloheptane; exact mass calculated for $C_{11}H_{23}N$, 169.1832; found, 169.1832.

The other imine components could not be collected in sufficient amounts and purity for full characterization; however, GC–MS showed them to have parent ions of 167, indicating them to be isomeric with **26**. Reduction of the crude imine product gave 63% of 2-butyl-7-methyl-1-azacycloheptane, which is in the reduction product of both **26** and **27**. Two other minor components were shown by GC–MS to have parent ions of 169; thus they are likely the reduction products of **28** and **29**. They were not further studied. Use of KH as described above gave a mixture of the imine products in 54% yield.

Acknowledgment. This work was supported by the National Science Foundation (Grant CHE 83-04000), whom we thank. G.A.B. was the recipient of an NSF Graduate Fellowship which also facilitated this study.

Registry No. **1**, 6526-78-9; **1a**, 96913-39-2; **2**, 2626-61-1; **2a**, 114635-54-0; **3**, 19165-94-7; **3a**, 114635-55-1; **4**, 40571-45-7; **4a**, 114635-56-2; **5**, 68288-41-5; **5a**, 114635-57-3; **6**, 19165-95-8; **6a**, 114635-58-4; **7**, 51655-31-3; **7a**, 114635-59-5; **8**, 114635-60-8; **8**·HCl, 114635-61-9; **8a**, 114635-62-0; **9**, 114635-63-1; **9**·HCl, 114635-64-2; **9a**, 114635-65-3; **10**, 114635-66-4; **10**·HCl, 114635-67-5; **10a**, 114635-68-6; **11**, 3338-03-2; **12**, 3338-06-5; **13**, 3338-08-7; **14**, 1462-92-6; **15**, 1462-94-8; **16**, 95018-41-0; **17a**, 114635-69-7; **17b**, 114635-70-0; **21**, 114635-71-1; **22**, 114635-72-2; **23**, 114635-73-3; **23**·K, 114635-74-4; **24**, 114635-75-5; **25**, 114635-76-6; **26**, 114635-77-7; **27**, 114635-78-8; **28**, 114635-79-9; **29**, 114635-80-2; *p*-NBSP, 6209-72-9; *m*-TFBSP, 35673-10-0; *N*-phenylcyclohexylimine, 1132-38-3; *n*-butylmagnesium bromide, 693-03-8; 2-methylcyclohexanone, 583-60-8; 2-(*n*-butyl)-1-methylcyclohexylamine, 114635-81-3; 2-methylcyclopentanone, 1120-72-5; 3-methylcyclohexanone, 591-24-2; 1-benzyl-1-nitrocyclohexane, 70367-75-8; 1-butyl-1-nitrocyclohexane, 92540-95-9; 1-butyl-2-methyl-1-nitrocyclohexane, 114635-82-4; 2-benzylazocycloheptane, 68840-81-3; *p*-nitrobenzoyl chloride, 122-04-3; 1-(*p*-nitrobenzoyl)-2-benzylazacycloheptane, 114635-83-5; *p*-nitrobenzenesulfonyl chloride, 98-74-8; 2-butyl-7-methyl-1-azocycloheptane, 114635-84-6.

Oxiranes from Methylenation of the Ester Carbonyl Group by Diazomethane

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Esters suitably substituted by electronegative groups were found to react with diazomethane with the anchimeric assistance of a π-system or a trifluoromethyl group close to the ester oxygen to yield 2-alkoxy-2-substituted-oxiranes in good to excellent yields without catalysts.

The addition of methylene to the carbonyl π-bond (1) of aldehydes and ketones with diazomethane to yield homologated carbonyl compounds and/or oxiranes is well established.[1] On the other hand, there are only two recorded instances of the latter reaction with the ester carbonyl, one in which diazoethane reacted with a complex lactone, i.e., a pyrazoline derivative of 3-nitrocoumarin (unreported yield),[2] and the other upon irradiation of a diazomethane solution containing methyl formate or acetate.[3]

The initial step is assumed to be the nucleophilic attack of the diazoalkane on the carbonyl to yield the zwitterion

(1) See, for example: *Advanced Organic Chemistry*; March, J.; Wiley: New York, 1985; pp 866 and 976. *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; Wiley: New York, 1978; pp 575 and 598. *Methoden Der Organischen Chemie, Houben-Weyl*; Müller, E., Ed.; G. Thieme Verlag: Stuttgart, 1976; Vol. VII/2b (Ketone), Part II, p 1855. *Methoden Der Organischen Chemie, Houben-Weyl*; Müller, E., Ed.; G. Thieme Verlag: Stuttgart, 1968; Vol. X/4 (Stickstoff-Verbindungen I), Part IV, p 712.

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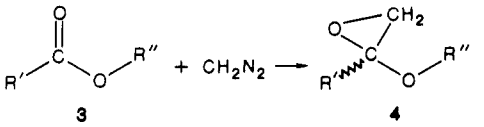
0022-3263/88/1953-3321$01.50/0

Table I. Reactions of Esters with Diazomethane

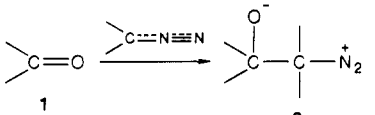


3 4

substrate	R′	R″	time[a] (h)	molar excess of CH_2N_2	% yield of 4[b] A	% yield of 4[b] B	bp (°C, Torr)
a	CF_3	C_6H_5	2	0.1	96	68	30, 1
b	CH_3	C_6H_5	20	9.0	0		
c	$C(CH_3)_2NO_2$	C_6H_5	20	9.0	0		
d	CH_2Cl	C_6H_5	20	9.0	0		
e	$CHCl_2$	C_6H_5	20	9.0	0.3[c]		
f	CF_3	$4\text{-}NO_2C_6H_4$	1	0.1	96	40[d]	93, 0.2
g	CH_3	$4\text{-}NO_2C_6H_4$	20	9.0	0		
h	CH_3	C_6F_5	20	9.0	0		
i	CF_3	$1\text{-}C_{10}H_7$	2	0.1	98	89	103, 0.2
j	CF_3	$2\text{-}C_{10}H_7$	2	0.1	95	51	110, 0.1
k	CF_3	1-cyclohexenyl	20	0.1	92[e]	56	82, 20
l	CCl_3	C_6H_5	12	0.1	98	76	86, 0.1
m	CF_3	CH_2CF_3	1	0.1	98	88	18, 60
n	CF_3	$1\text{-}C_6H_{13}$	20	9.0	<1		
o	CF_3	cyclohexyl	20	9.0	<1		
p	CF_3	2-cyclohexenyl	20	9.0	<1		
q	C_6F_5	CH_3	20	9.0	0		
r	CF_3	benzyl	20	9.0	32[f]		
s	C_6H_5	$CH(CF_3)_2$	20	9.0	0		
t	C_6H_5	CH_2CF_3	20	9.0	0		
u	CF_3	$4\text{-}CH_3OC_6H_4$	12	0.1	98	72	64, 4

[a] The reactions were monitored by GC–MS: those that proceeded at a reasonable speed were stopped at practical completion. [b] A: determined by GC using the internal standard method. B: separated by conventional distillation on a 3–5-g scale. [c] Also phenol (3%). [d] The product was very sensitive to moisture, yielding 4-nitrophenol: it partially decomposed during distillation. [e] Also cyclohexanone (6%). [f] Also benzyl alcohol (11%).

2, which loses nitrogen either with a concomitant ring closure or by a 1,2-shift of a neighboring group.



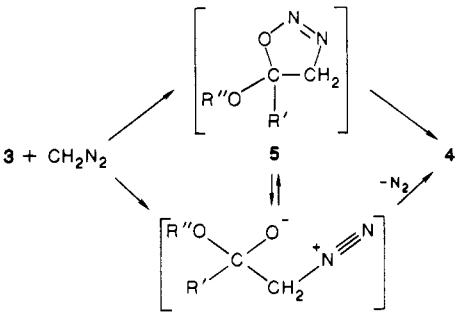
1 2

Following a preliminary observation[4] of the facile methylenation of the carbonyl group of phenyl trifluoroacetate (**3a**) by CH_2N_2 in ether at room temperature in the dark to yield **4a**, we have now performed a number of experiments to define the scope and requirements for this reaction.

The preliminary task was to determine the role of R′ and R″ (see Table I) in the reaction. The variations of the acyl group of phenyl esters (R″ = C_6H_5) established the absolute need of enough electron-withdrawing power for the reaction to go. In fact, phenyl acetate (**3b**) proved to be quite unreactive, and a single nitro group (**3c**) or chlorine (**3d**) substituent was definitely not adequate, whereas two chlorine atoms (**3e**) led only to very slow reaction. Electron-withdrawing power may be added from the phenyl side (4-NO_2, **3f**) to strongly accelerate the reaction, but again it was inadequate by itself alone (R′ = CH_3; R″ = $4\text{-}NO_2C_6H_4$, **3g**, or R″ = C_6F_5, **3h**).

Since carbonyl addition of diazomethane occurred readily with aryl trifluoroacetates (**3a,i,j**), we examined the role of other π-electron systems in the R″ group and found that a single double bond attached directly to the ester

Scheme I



oxygen (**3k**) was sufficient to promote the reaction.

It was put forward[2] that the role of the electron-rich, but also electron-withdrawing, nitro group was that of solvating the postulated open chain cationic diazo derivative intermediate **2**. Our results give a more complete and detailed picture for this assumption. Electron-withdrawing α-substituents on the acyl side as well as on the aryl ether (4-NO_2, **3f**) moiety play an essential role in activating kinetically and probably shifting more to the right the initial step of the process by making the carbonyl carbon atom more positive. However, the successful completion of the reaction is assured by the presence of unsaturation directly linked to the ether oxygen or of a trifluoromethyl group close to the ester α-carbon, as in 2,2,2-trifluoroethyl trifluoroacetate (**3m**). On the other hand, alkyl trifluoroacetates (**3n–p**) or methyl pentafluorobenzoate (**3q**) were practically unreactive toward CH_2N_2, even when present in large excess. Nitrogen loss and ring closure to oxiranes may occur by some form of charge-transfer interaction between the N_2^+ group and the unsaturation, or by some internal solvation effect, possibly leading to the transient formation of a cyclic intermediate like **5** (Scheme

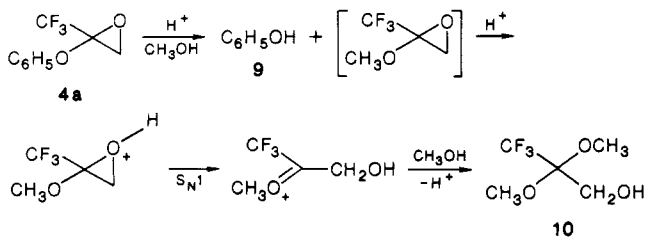
(4) For a preliminary report on this work, see: Verardo, G.; Strazzolini, P.; Giumanini, A. G. *Tetrahedron Lett.* **1987**, *28*, 3011. Presented in part at the Convegno Nazionale della Divisione di Chimica Organica of the Società Chimica Italiana, Fiuggi, FR, I, September 13–18, 1987; poster communication p 42.

I). The latter hypothesis received some support by the observation of the decreasing effectiveness for oxirane formation in the sequence **3a**, **3k**, and **3r**, the last one being much less reactive.

The importance of having an electron-deficient carbonyl carbon for the reaction was additionally evidenced by the inertness of some trifluoroacetamides, like *N*-methyl-*N*-(trifluoroacetyl)aniline (**6**), its 4-nitro derivative **7**, and the less likely *N*-(trifluoroacetyl)morpholine (**8**); removal of the trifluoromethyl group from close proximity of the carbonyl with concomitant switching of positions with an aryl group, as in 1,1,1,3,3,3-hexafluoro-2-propyl benzoate (**3s**) and 2,2,2-trifluoroethyl benzoate (**3t**), quenched any reactivity of the kind (Table I).

Competition Experiments. Competition experiments were performed in which two esters competed for a deficient amount of diazomethane in order to have a rough indication of the relative reactivities for systems that did not give side products. The relative amounts of **4** formed were hinted at by a GC trace using the total ion monitor of a mass spectrometer as detector. The relative reactivities were found to be **3f** ≫ **3a** > **3u** ≫ **3k**.

Structural Identification and Properties of 4. The reaction products **4** showed a reasonable thermal stability: all of them could be distilled in vacuo without decomposition, but they are labile under hydrolytic conditions.[4] Acidic methanolysis of **4a** gave a quantitative yield of phenol (**9**) and a more volatile compound, whose mass



spectrum, recorded from the eluate from gas chromatography, could be reconciled with the expected fragmentations of 3,3,3-trifluoro-2,2-dimethoxypropanol (**10**), i.e., a weak parent ion (at *m/e* 174) and peaks at 143 (loss of CH_3O and/or CH_2OH), 129 (CH_3, CHO), and 109 (loss of HF from 129). The peaks at *m/e* 46 and 45 would be rationalized in terms of loss of dimethyl ether from the ion at 143, a behavior observed previously in the positive ion chemistry of methyl orthoformate.[5] This identification, which could not be further supported by derivative formation or actual separation due to the chemical lability of the compound, is in agreement with previous findings[3,6] about the chemical behavior of alkoxyoxiranes.

Very minor amounts (less than 1%) of double addition of a methylene group could be observed in the GC–MS analysis of the crude reaction mixtures: they were lost in the workup for the separation of **4**.

Conclusion

The net addition of a methylene across the ester carbonyl using diazomethane may be achieved in the absence of any catalyst with ease and good to excellent yields and relatively short reaction times provided enough electrophilicity is accumulated on the carbon atom by electron-withdrawing groups, and, in addition, assistance by a close π-system or trifluoromethyl group is necessary.

Experimental Section[7]

Trifluoroacetates **3a**,[1] **3f**,[8] **3i**,[9] **3j**,[10] **3n**,[11] **3o**,[12] **3p**,[13] **3r**,[12] and **3u**[14] were all known products. They were prepared for this work by the reaction of trifluoroacetic anhydride (TFAA) with the corresponding hydroxy compounds in chilled ether solution during 1 h). The pure products were isolated by conventional distillation. Physical properties of **3p**: bp 44 °C (10 Torr); ^{1}H NMR 1.40–2.50 (m, 6 H) and 5.20–6.40 ppm (m, 3 H); IR (neat) 3045 (w), 2960 (m), 2880 (w), 1785 (vs), 1655 (w), 1460–1430 (w), 1382 (s), 1350 (m), 1322 (m), 1153 (vs), 1180–1140 (vs), 1100 (w), 1050 (m), 1008 (w), 997 (w), 940 (w), 924 (w), 898 (vs), 860 (w), 831 (w), 822 (w), 773 (m), 729 (w), 719 (m), 670 (w), and 520 (w) cm^{-1}; MS, *m/e* 80 (100), 69 (33), 41 (29), 39 (28), 53 (21), 97 (6), and 194 (M^+, 0.2). Anal. Calcd for $C_8H_9F_3O_2$: C, 49.49; H, 4.67. Found: C, 49.54; H, 4.68. Product **3p** acquired a violet color on standing for several days at room temperature in the dark.

1-(Trifluoroacetoxy)cyclohexene (3k)[15] was prepared according to a previously described procedure:[16] the reaction mixture of trifluoroacetyl triflate, 2,6-di-*tert*-butyl-4-methylpyridine, and cyclohexanone in dry CH_2Cl_2 was stirred during 16 h at 0 °C with formation of a colorless precipitate, which was separated (2,6-di-*tert*-butyl-4-methylpyridinium triflate). The brownish clear solution obtained was concentrated in vacuo, and dry ether was added, causing further precipitation of the amine salt. The residual solution was washed with water and a solution of sodium metabisulfite until cyclohexanone was no longer present (GC). The dried (Na_2SO_4) solution was then distilled, bp 61 °C at 30 Torr (lit.[15] bp 64–66 °C at 40 Torr), to give a GC homogenous colorless liquid (yield 75%, 3.5-g preparation). GC conditions: injector at 150 °C, column isotherm at 60 °C. The ^{1}H NMR spectrum was in agreement with the literature data.[16] IR (neat): 2935 (s), 2865 (w), 2845 (w), 1798 (vs), 1692 (m), 1461 (w), 1442 (m), 1417 (w), 1362 (s), 1338 (m), 1295 (w), 1223 (s), 1180–1130 (vs), 1087 (m), 1071 (m), 1040 (w), 968 (w), 984 (w), 925 (m), 889 (s), 856 (w), 824 (w), 800 (m), 792 (w), 762 (s), 736 (m), 725 (m), 645 (w), and 610 (w) cm^{-1}; MS, *m/e* 79 (100), 41 (72), 69 (67), 80 (59), 55 (51), 194 (M^+, 25), and 97 (15). Anal. Calcd for $C_8H_9F_3O_2$: C, 49.49; H, 4.67. Found: C, 49.59; H, 4.69. Product **3k** acquired a violet color on standing for several days at room temperature in the dark.

2,2,2-Trifluoroethyl trifluoroacetate (3m)[17] was prepared by mixing a slight excess of trifluoroacetic anhydride with 2,2,2-trifluoroethanol with cooling under anhdyrous conditions. The clear colorless mixture obtained was refluxed for 5 h and left standing overnight at room temperature. The reaction mixture was then dropped on a stoichiometric amount of anhydrous calcium carbonate and stirred at room temperature during 1 h.

(5) *Mass Spectrometry of Organic Compounds*; Budzikiewicz, H.; Djerassi, C.; Williams, D. H.; Holden-Day: San Francisco, 1967; p 268.
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(7) Elemental analyses were performed on a Carlo Erba elemental analyzer Model 1106. Melting and boiling points are uncorrected. Proton magnetic resonance spectra ($CDCl_3$ solvent, TMS as internal standard) were recorded on a Bruker WP 80 SY nuclear magnetic resonance spectrometer. Infrared spectra were recorded on a JASCO DS-702G infrared spectrometer either neat on potassium bromide plates (for oils and liquids) or as potassium bromide pellets (for solids). Mass spectra were obtained at 70 eV with GC inlet (Supelco SPB-5 30-m fused silica capillary column) on a Finnigan 1020 quadrupole GC–MS apparatus: the five most intense peaks are reported with intensities in parentheses in addition to the molecular mass and other less intense peaks when suitable. When clusters of parent ions show up in mass spectra due to the material isotopic composition, the lowest mass only is reported. Chemicals for which the synthesis is not reported were commercially available.
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The ester **3m** was obtained by distillation and collected on anhydrous Na_2SO_4: bp 55 °C at 760 Torr (lit.[17] bp 57 °C); yield 87%, 6.8-g preparation. GC conditions: injector at 150 °C, column isotherm at 50 °C. The ^1H NMR, IR (neat), and mass spectra were in agreement with the literature data.[17]

Phenyl esters of $CCl_nH_{3-n}COOH$ (3b, 3d,[18] 3e,[18] and 3l[18]) and pentafluorophenyl acetate (3h)[19] were prepared from the corresponding acyl chlorides and **9** or pentafluorophenol in the presence of triethylamine (TEA) in dry ether at room temperature (1 h) in practically quantitative GC yields. MS: **3b** (n = 0), m/e 94 (100), 43 (49), 39 (32), 66 (30), 65 (26), and 136 (M^+, 18); **3d** (n = 1), m/e 94 (100), 39 (57), 65 (52), 77 (51), 49 (40), and 170 (M^+, 13); **3e** (n = 2), m/e 94 (100), 77 (65), 65 (47), 83 (39), 39 (36), and 204 (M^+, 25); **3l** (n = 3), m/e 77 (100), 117 (67), 119 (65), 65 (64), 121 (63), and 238 (M^+, 50); **3h**, m/e 43 (100), 42 (52), 155 (46), 69 (41), 117 (39), 184 (38), and 226 (M^+, 2).

2,2,2-Trifluoroethyl benzoate (3t)[12] **and 1,1,1,3,3,3-hexafluoro-2-propyl benzoate (3s)**[20] were prepared from the corresponding commercial (Aldrich) alcohols and benzoyl chloride, in the presence of TEA in dry ether (1 h, room temperature), according to standard procedures. MS: **3t**, m/e 105 (100), 77 (80), 51 (58), 204 (M^+, 48), and 50 (28); **3s**, m/e 105 (100), 77 (83), 51 (61), 69 (45), 50 (41), and 272 (M^+, 28).

Methyl pentafluorobenzoate (3q)[21] was prepared by adding a slight excess of ethereal pentafluorobenzoyl chloride (Aldrich) to a solution of methanol in dry ether containing an equimolecular amount of anhydrous K_2CO_3. The reaction mixture was refluxed for 2 h, filtered, dried over Na_2SO_4, and evaporated to dryness. The oily residue was fractionally distilled, giving the pure ester: bp 44 °C at 4 Torr; yield 90% (4.4-g preparation); ^1H NMR 3.99 ppm (s, 3 H); IR (neat) 2960 (w), 1742 (s), 1650 (m), 1496 (s), 1437 (m), 1419 (w), 1330 (s), 1234 (s), 1145 (w), 1100 (w), 1007 (s), 975 (m), 888 (w), 807 (w), and 755 (m) cm^{-1}; MS, m/e 195 (100), 117 (68), 167 (53), 226 (M^+, 25), and 93 (23). Anal. Calcd for $C_8H_3F_5O_2$: C, 42.50; H, 1.34. Found: C, 42.61; H, 1.34.

Phenyl 2-Methyl-2-nitropropanoate (3c). Phenyl 2-bromo-2-methylpropanoate[22] [bp 78 °C at 0.2 Torr (lit. bp 157 °C at 42 Torr); ^1H NMR 2.06 (s, 6 H) and 7.00–7.60 ppm (m, 5 H); IR (neat) 3065 (vw), 3005 (w), 2975 (w), 2925 (w), 1755 (vs), 1592 (s), 1490 (s), 1460 (s), 1389 (m), 1371 (m), 1260 (s), 1200–1180 (s), 1160 (s), 1133 (s), 1100 (s), 1067 (m), 1021 (w), 1006 (m), 937 (m), 908 (w), 851 (w), 820 (m), 810 (w), 737 (s), 681 (s), and 648 (w) cm^{-1}; MS, m/e 94 (100), 41 (47), 39 (38), 121 (32), 123 (30), and 242 (M^+, 4)] was transformed into **3c** according to a general procedure,[23] yielding **3c** as a GC homogeneous yellow oil (crude yield 100%), distilling at 90–92 °C at 0.2 Torr: ^1H NMR 1.93 (s, 6 H) and 6.95–7.65 ppm (m, 5 H); IR (neat) 3070 (w), 3005 (w), 2955 (w), 2895 (w), 1776 (vs), 1595 (s), 1555 (vs), 1494 (s), 1465 (s), 1400 (s), 1375 (m), 1348 (s), 1272 (s), 1191 (vs), 1168 (s), 1133 (vs), 1071 (m), 1024 (m), 1008 (w), 954 (w), 918 (m), 870 (m), 850 (m), 826 (w), 810 (m), 746 (s), 728 (w), and 686 (s) cm^{-1}; MS, m/e 93 (100), 70 (95), 41 (90), 65 (88), 39 (83), and 209 (M^+, 24). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.49; H, 5.32; N, 6.69.

Trifluoroacetamides 6,[24] 7,[25] and 8[24] were prepared by adding a slight excess (ca. 10%) of TFAA dropwise to a chilled and stirred ether solution of the corresponding amines (30 min): the GC pure amides were obtained by conventional distillation.

Reaction of Ester and Amide Substrates with Diazomethane. In a typical experiment the substrate was treated with ca. 10% molar excess of CH_2N_2[26] in ether at room temperature and in the dark for a suitable time. The course of the reactions was monitored by capillary GC–MS. The reaction mixtures were then concentrated, washed with 0.1 M aqueous sodium hydroxide, dried (Na_2SO_4), and distilled to separate the product formed. In case of either no or sluggish reaction a 10-fold excess of CH_2N_2 was used to try to force the event. The results are summarized in Table I.

CAUTION. Some of the oxiranes **4** were found to be strongly lacrymatory.

2-(Trifluoromethyl)-2-phenoxyoxirane (4a): ^1H NMR 2.91–3.03 (m, 1 H), 3.10 (d, 1 H), and 7.03–7.39 ppm (m, 5 H); IR (neat) 3080 (w), 3050 (w), 3025 (vw), 1598 (s), 1497 (s), 1460 (w), 1414 (m), 1327 (s), 1220–1150 (vs), 1112 (s), 1075 (w), 1023 (w), 1002 (m), 947 (w), 924 (s), 908 (w), 835 (m), 810 (w), 764 (m), 727 (w), 689 (s), 642 (w), 612 (w), 593 (w), 560 (w), and 490 (m) cm^{-1}; MS, m/e 77 (100), 65 (47), 204 (M^+, 42), 90 (30), and 51 (29). Anal. Calcd for $C_9H_7F_3O_2$: C, 52.95; H, 3.46. Found: C, 52.99; H, 3.47.

2-(Trifluoromethyl)-2-(4-nitrophenoxy)oxirane (4f): ^1H NMR 3.13–3.27 (m, 1 H), 3.33 (d, 1 H), and 7.12–8.40 ppm (m, 5 H); IR (neat) 3120 (w), 3090 (w), 1617 (m), 1597 (s), 1520 (s), 1492 (s), 1407 (w), 1350 (s), 1330 (m), 1317 (m), 1230 (vs), 1200–1170 (vs), 1152 (m), 1110 (vs), 1032 (w), 1010 (w), 930 (w), 918 (w), 858 (m), 848 (m), 827 (w), 808 (w), 743 (m), 690 (w), 637 (w), 612 (w), and 484 (w) cm^{-1}; MS, m/e 63 (100), 69 (99), 64 (89), 75 (81), 50 (81), and 249 (M^+, 41). Anal. Calcd for $C_9H_6F_3NO_4$: C, 43.38; H, 2.43; N, 5.62. Found: C, 43.47; H, 2.43; N, 5.60.

2-(Trifluoromethyl)-2-(1-naphthoxy)oxirane (4i): ^1H NMR 2.75–2.89 (m, 1 H), 3.05 (d, 1 H), and 7.10–8.40 ppm (m, 7 H); IR (neat) 3065 (w), 3020 (w), 2985 (w), 1638 (w), 1603 (m), 1581 (w), 1512 (w), 1487 (w), 1468 (w), 1417 (m), 1397 (s), 1322 (s), 1263 (s), 1235 (s), 1210–1170 (vs), 1152 (s), 1120 (vs), 1082 (w), 1018 (m), 996 (m), 919 (m), 863 (w), 854 (w), 825 (m), 796 (s), 770 (s), 748 (m), 672 (w), 602 (w), 555 (w), and 418 (w) cm^{-1}; MS, m/e 115 (100), 143 (53), 254 (M^+, 50), 127 (40), and 69 (25). Anal. Calcd for $C_{13}H_9F_3O_2$: C, 61.42; H, 3.57. Found: C, 61.45; H, 3.58.

2-(Trifluoromethyl)-2-(2-naphthoxy)oxirane (4j): ^1H NMR 2.89–3.03 (m, 1 H), 3.09 (d, 1 H), and 7.09–7.88 ppm (m, 7 H); IR (neat) 3065 (w), 3025 (vw), 2920 (vw), 1637 (m), 1605 (m), 1512 (m), 1482 (w), 1469 (m), 1443 (w), 1415 (m), 1358 (w), 1321 (s), 1268 (w), 1248 (m), 1220–1150 (vs), 1126 (m), 1108 (s), 999 (m), 964 (m), 923 (m), 899 (w), 892 (m), 850 (m), 823 (w), 807 (m), 746 (s), 669 (w), 608 (w), and 470 (m) cm^{-1}; MS, m/e 115 (100), 127 (64), 254 (M^+, 57), 141 (29), and 69 (23). Anal. Calcd for $C_{13}H_9F_3O_2$: C, 61.42; H, 3.57. Found: C, 61.49; H, 3.58.

2-(Trifluoromethyl)-2-(1-cyclohexenyloxy)oxirane (4k): ^1H NMR 1.35–2.25 (m, 8 H), 3.06–3.26 (m, 2 H), and 5.20–5.38 ppm (m, 1 H); IR (neat) 3080 (vw), 3025 (vw), 2845 (s), 2870 (w), 2855 (w), 1685 (m), 1486 (w), 1448 (w), 1412 (m), 1369 (w), 1325 (s), 1269 (w), 1210–1130 (vs), 1110 (s), 1048 (w), 1028 (m), 1000 (m), 978 (w), 909 (m), 900 (m), 853 (w), 826 (m), 796 (w), 780 (w), 741 (w), 732 (w), and 623 (w) cm^{-1}; MS, m/e 41 (100), 81 (81), 79 (80), 55 (78), 53 (68), 69 (64), and 208 (M^+, 14). Anal. Calcd for $C_9H_{11}F_3O_2$: C, 51.92; H, 5.33. Found: C, 52.00; H, 5.35.

2-(Trifluoromethyl)-2-(2,2,2-trifluoroethoxy)oxirane (4m): GC conditions, injector at 150 °C, column isotherm at 50 °C; ^1H NMR 3.16–3.24 (m, 2 H) and 3.86–4.22 ppm (pseudo q, 2 H); IR (neat) 3025 (w), 2965 (m), 2900 (vw), 1480 (w), 1455 (w), 1415 (s), 1335 (s), 1275 (s), 1170 (vs), 1128 (s), 1112 (s), 1070 (m), 1008 (m), 990 (w), 962 (m), 907 (m), 825 (s), 745 (m), 665 (w), 590 (m), and 552 (w) cm^{-1}; MS, m/e 112 (100), 64 (67), 69 (66), 83 (60), 61 (48), and 210 (M^+, 34). Anal. Calcd for $C_5H_4F_6O_2$: C, 28.59; H, 1.92. Found: C, 28.51; H, 1.92.

2-(Trifluoromethyl)-2-(4-methoxyphenoxy)oxirane (4u): ^1H NMR 2.87–3.01 (m, 1 H), 3.06 (d, 1 H), 3.75 (s, 3 H), and 6.69–7.16 ppm (m, 4 H); IR (neat) 3005 (w), 2960 (w), 2915 (w), 2840 (w), 1612 (w), 1598 (w), 1510 (s), 1487 (w), 1469 (w), 1445

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(26) *Chimica Organica Pratica*; Vogel, A. I.; CEA: Milano, 1967; p 977 (preparation using 2-(2-ethoxyethoxy)ethanol). In order to allow for a handier product GC–MS detection and separation in the case of the reaction between **3m** and CH_2N_2, the latter reagent was prepared and codistilled with trichlorofluoromethane (Freon 11, Aldrich, bp 23.7 °C) instead of the traditional diethyl ether: the obtained diazomethane solution has a much lower content of water, but the reactant seems much less stable toward decomposition.

(w), 1414 (m), 1325 (s), 1300 (m), 1251 (s), 1220–1150 (vs), 1111 (s), 1032 (s), 997 (w), 930 (w), 912 (w), 845 (m), 837 (m), 760 (m), 728 (w), 700 (w), and 514 (w) cm^{-1}; MS, *m/e* 123 (100), 95 (40), 121 (27), 77 (26), and 234 (M^+, 22). Anal. Calcd for $C_{10}H_9F_3O_3$: C, 51.29; H, 3.87. Found: C, 51.41; H, 3.88.

2-(Trichloromethyl)-2-phenoxyoxirane (4l): ^1H NMR 3.04 (d, 1 H, J_{AB} = 3.21 Hz), 3.50 (d, 1 H, J_{AB} = 3.21 Hz), and 6.85–7.48 ppm (m, 5 H); IR (neat) 3065 (w), 3040 (w), 1593 (m), 1491 (s), 1455 (w), 1355 (m), 1290 (w), 1225 (vs), 1160 (w), 1140 (w), 1084 (w), 1070 (w), 1020 (w), 995 (w), 920 (s), 838 (w), 800–780 (vs), 760 (w), 730 (m), 668 (s), 628 (w), 552 (w), and 488 (w) cm^{-1}; MS, *m/e* 77 (100), 65 (98), 79 (89), 107 (88), 51 (67), and 252 (M^+, 29). Anal. Calcd for $C_9H_7Cl_3O_2$: C, 42.64; H, 2.78. Found: C, 42.69; H, 2.78.

Methanolysis of 4a. The oxirane **4a** (ca. 20 mg) was treated with 1 mM methanolic hydrogen chloride in a sealed tube at 70 °C during 1 h in a nitrogen atmosphere. The reaction mixture was directly analyzed by GC–MS; the oxirane **4a** had reacted completely to yield quantitatively **9** and a more volatile compound **10**: MS, *m/e* 45 (100), 46 (53), 129 (42), 59 (31), 109 (29), 63 (23), 69 (20), 95 (17), 143 (9), 105 (8), 157 (2), and 174 (M^+, 0.4).

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Registry No. **3a**, 500-73-2; **3b**, 122-79-2; **3c**, 114397-39-6; **3d**, 620-73-5; **3e**, 10565-20-5; **3f**, 658-78-6; **3g**, 830-03-5; **3h**, 19220-93-0; **3i**, 41190-40-3; **3j**, 398-49-2; **3k**, 42872-38-8; **3l**, 10112-13-7; **3m**, 407-38-5; **3n**, 400-61-3; **3o**, 1549-45-7; **3p**, 64487-54-3; **3q**, 36629-42-2; **3r**, 351-70-2; **3s**, 10315-85-2; **3t**, 1579-72-2; **3u**, 5672-87-7; **4a**, 113200-26-3; **4e**, 114397-40-9; **4f**, 114397-41-0; **4i**, 114397-42-1; **4j**, 114397-43-2; **4k**, 114397-44-3; **4l**, 114397-45-4; **4m**, 114397-46-5; **4r**, 114397-47-6; **4u**, 114397-48-7; **6**, 345-81-3; **7**, 39651-54-2; **8**, 360-95-2; **9**, 108-95-2; **10**, 114397-49-8; 4-$O_2NC_6H_4OH$, 100-02-7; $C_6H_5CH_2OH$, 100-51-6; CH_2N_2, 334-88-3; F_3CCH_2OH, 75-89-8; 1-$C_{10}H_7OH$, 90-15-3; 2-$C_{10}H_7OH$, 135-19-3; $C_6H_{13}OH$, 111-27-3; 4-$H_3COC_6H_4OH$, 150-76-5; $ClCH_2COCl$, 79-04-9; $Cl_2CHCOCl$, 79-36-7; CCl_3COCl, 76-02-8; C_6F_5OH, 771-61-9; H_3CCOCl, 75-36-5; cyclohexanone, 108-94-1; cyclohexanol, 108-93-0; 2-cyclohexen-1-ol, 822-67-3; 1,1,1,3,3,3-hexafluoro-2-propanol, 920-66-1; benzoyl chloride, 98-88-4; pentafluorobenzoyl chloride, 2251-50-5; phenyl 2-bromo-2-methylpropanoate, 114397-50-1; *N*-methylaniline, 100-61-8; *N*-methyl-4-nitroaniline, 100-15-2; morpholine, 110-91-8.

Quinolizidine Synthesis via Intramolecular Immonium Ion Based Diels–Alder Reactions: Total Syntheses of (±)-Lupinine, (±)-Epilupinine, (±)-Cryptopleurine, and (±)-Julandine†

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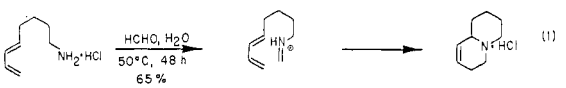
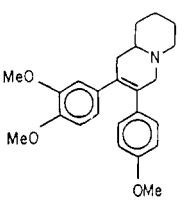
Total syntheses of (±)-julandine (**1**), (±)-cryptopleurine (**2**), (±)-lupinine (**3**), and (±)-epilupinine (**4**) have been developed that feature intramolecular immonium ion based Diels–Alder reactions. Amines **6** and **14**, prepared from stilbene ester **5** in a straightforward manner, gave rise to, upon treatment with aqueous formaldehyde solution, the corresponding immonium salts, which undergo intramolecular cyclocondensation, leading to isojulandine (**11**) and cryptopleurine (**2**), respectively, in good yield. Exposure of **11** to acid afforded (±)-julandine. Intramolecular [4 + 2] cycloaddition of immonium ion **18** derived from amine **17** provided Diels–Alder adducts **19** and **20**, which are rationalized on the basis of transition states **22** and **23**, respectively. Reduction of **19** and **20** gave (±)-epilupinine (**4**) and (±)-lupinine (**3**), respectively.

The feasibility of employing an intramolecular immonium ion based Diels–Alder reaction for the construction of quinolizidine alkaloids was established during our preliminary study on the cyclocondensation of immonium salts with dienes under Mannich-like conditions (cf. eq 1).[2]



(1)

As an extension of this work, we set out to apply this methodology to the synthesis of naturally occurring alkaloids. Accordingly, we detail below the total synthesis of (±)-julandine (**1**)[3] and (±)-cryptopleurine (**2**).[3,4] In addition, studies to establish whether side-chain stereochemistry might be controlled in the construction of octahydroquinolizidines have also been examined. In this regard the total syntheses of (±)-lupinine (**3**) and (±)-epilupinine (**4**)[4,5] are described.



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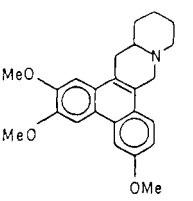

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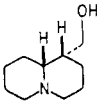

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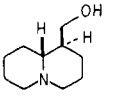

4

In order to probe the application of the immonium ion based Diels–Alder strategy to the construction of julandine,

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

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