Lewis Acid-induced Ene-Cyclization of ω-Olefinic Trifluoromethyl Ketones: Access to Alicyclic Compounds bearing a CF_3 Group

Ahmed Abouabdellah,[a] Corinne Aubert,[a] Jean-Pierre Bégué,*[a] Danièle Bonnet-Delpon[a] and Jean Guilhem[b]
[a] *CNRS-CERCOA, 2, Rue H. Dunant, 94320 Thiais, France*
[b] *CNRS-ICSN, 91198 Gif-sur-Yvette Cedex, France*

Several catalysts (Me_2AlCl, $MeAlCl_2$, $EtAlCl_2$ and $TiCl_4$) for the ene carbocyclization of olefinic trifluoromethyl ketonic compounds have been compared. Thus, five-, six-, seven- and eight-membered-ring compounds were obtained. Olefin regiochemistry and stereoselectivity are better controlled than in related non-fluorinated series. High yields of cyclic trifluoromethyl alcohols were obtained by the achievement of type-I, -II or -III ene processes, concerted or otherwise. The first example of an eight-membered cyclization is described.

Much attention has been focused on trifluoromethyl compounds owing to their biological significance.[1] The selective introduction of a CF_3 group into organic molecules became a major goal in fluoroorganic chemistry. Since it is not easy to introduce directly a trifluoromethyl group in alicyclic rings, we became interested in the synthesis of CF_3-containing carbocycles through cyclization reactions.

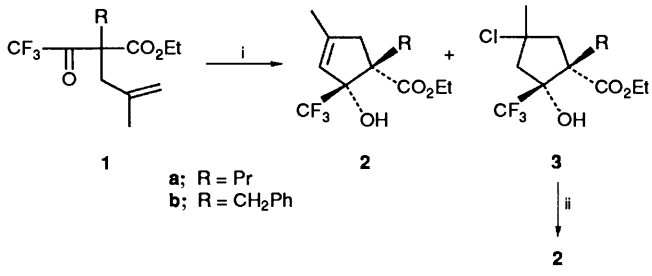
In spite of recent significant progress in radical cyclization,[2] carbocationic cyclization is a fruitful approach to the preparation of alicyclic compounds bearing a CF_3 group.[3,4] In this connection, a strategy involving the intramolecular cyclization of ω-unsaturated carbonyl compounds could allow easy access to functionalized alicyclic compounds. These Lewis acid-initiated ene reactions are well documented when they are performed with ω-unsaturated aldehydes.[5,6] However, few examples have been reported with ω-unsaturated ketones because of their lower reactivity.[7,8] Electron-deficient trifluoromethyl ketones turned out to be good enophiles for such Lewis acid-promoted ene reactions.[9,10] Reported herein are the results of a study of the ene-cyclization of some ω-unsaturated trifluoromethyl ketones and β-keto esters to prepare monocyclic (C_5–C_8) functional compounds bearing a CF_3 group.

Results

The starting materials **1a**, **1b**, **4a** and **4b** were prepared by direct alkylation of ethyl trifluoroacetoacetate (ETFAA).[11] The ketones **15b** and **15c** were obtained by alkylation of the dimethylhydrazone of ETFAA.[12] The ketones **15a** and **10b** were prepared by hydrolysis, in the presence of KF, of the corresponding trifluoromethyl silyl enol ether, obtained by Wittig reaction on trimethylsilyl trifluoroacetate, as we have previously described.[13] Ketones **10a** and **10b** were obtained from ketones **15a** and **15b** by acidic isomerization.[12]

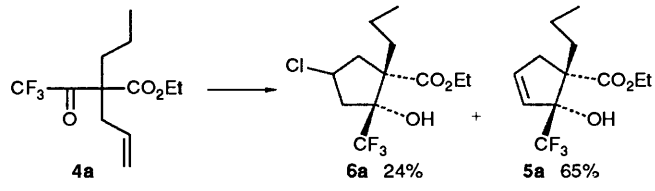
Formation of Five-membered Rings.—From β-keto esters **1a**, **1b**, **4a** *and* **4b**. The $EtAlCl_2$-initiated cyclization of compounds **1a** and **1b** provided a mixture of cyclopentene **2** and cyclopentane products **3** identified as chlorides; products **3** eliminate HCl completely to afford the cyclopentene **2** after purification (Scheme 1, Table 1: runs 1 and 3). When reactions were performed with $TiCl_4$, yields were improved to 80% for **2a** and >90% for **2b** (runs 2 and 4).

Complete reaction of substrate **4a** needed 4 mol equiv. of Lewis acid (Scheme 2). With $EtAlCl_2$, a 65% yield of two chlorides **6a** (80/20) were obtained in admixture with the cyclopentanol **5a** (15%) and reduced product **8** (15%) (run 6).



Scheme 1 *Reagents:* i, Lewis acid; ii, SiO_2 chromatography

With $TiCl_4$, reaction was slower and selectivity was different: the cyclopentenol **5a** was obtained as the major product (65%), together with a 24% yield of chlorides **6a** (85/15 mixture) (run 8).



Scheme 2 *Reagents and conditions:* $TiCl_4$ (4 mol equiv.), 0 °C

Cyclization of substrates **1a**, **1b** and **4a** is very stereoselective: IR spectral data (strong intramolecular H-bonding) show a *cis* relationship between the hydroxy and ethoxycarbonyl groups.[14] The position of the double bond was determined in compound **5a** by the presence of a J_{HF} coupling between 5-H and CF_3. This stereochemistry and the position of the double bond are confirmed unambiguously by the X-ray structure of the mono-*p*-nitrobenzoate **7b**, derived from diol **7a**, the reduction product of compound **2b** (Fig. 1).

Reaction of compound **4b** was complete with only 1 mol equiv. of $TiCl_4$, or 3 mol equiv. of $EtAlCl_2$, but the indanol **9** was obtained, instead of the expected monocycle derivatives **5b** and **6b** (Scheme 3, Table 1: runs 9–11).

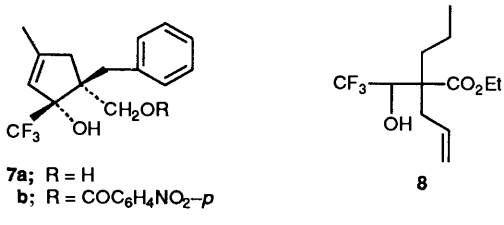


Table 1 Cyclization of β-keto esters **1a**, **1b**, **4a** and **4b**

Run	Compound	Lewis acid (mol equiv.)	Temp (T/°C) and time (t/h)	Products and yields (%)[a]		
1	**1a**	$EtAlCl_2$ (1.1)	0 (3.5)	**2a** 54 (80)	**3a**[b] 43 (0)	
2	**1a**	$TiCl_4$ (1.1)	0 (3.5)	**2a** 81 (75)	**3a**[b] 7 (0)	
3	**1b**	$EtAlCl_2$ (1.1)	0 (3.5)	**2b** 68 (80)	**3b**[b] 14 (0)	
4	**1b**	$TiCl_4$ (1.1)	0 (2)	**2b** 99 (90)		
5	**4a**	$EtAlCl_2$ (1.1)	20 (26)	**4a** 79	**6a** 6	**8** 9
6	**4a**	$EtAlCl_2$ (4)	0 (7)	**5a** 15 (10)	**6a** 65 (50)	**8** 15 (10)
7	**4a**	$TiCl_4$ (1.1)	0 (26)	**4a** 80	**5a** 12	**6a** 5
8	**4a**	$TiCl_4$ (4)	0 (26)	**5a** 64 (49)	**6a** 24 (20)	
9	**4b**	$EtAlCl_2$ (1.1)	0 (24)	**4b** 100		
10	**4b**	$EtAlCl_2$ (3)	0 (6)	**9** 85 (80)		
11	**4b**	$TiCl_4$ (1.1)	0 (3.5)	**9** 83 (77)		

[a] Estimated yields from GC analysis; the parenthetic values are isolated yields. [b] Products **3a** and **3b** are unstable and give compounds **2a** and **2b** when eluted on SiO_2

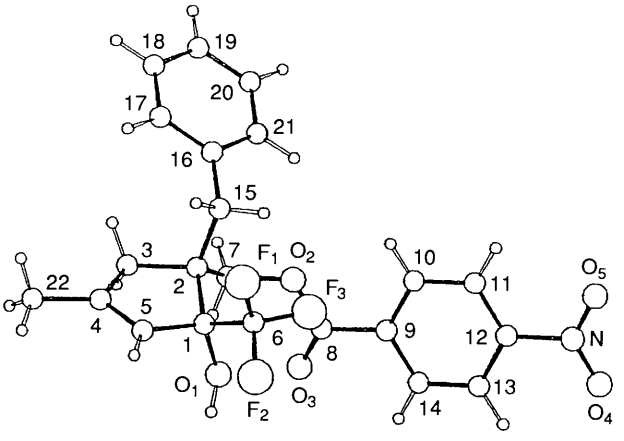
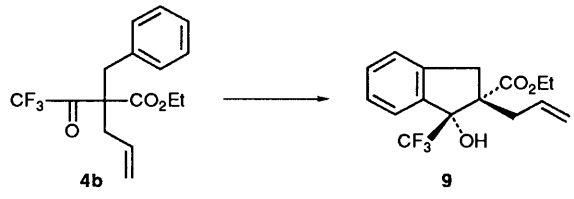
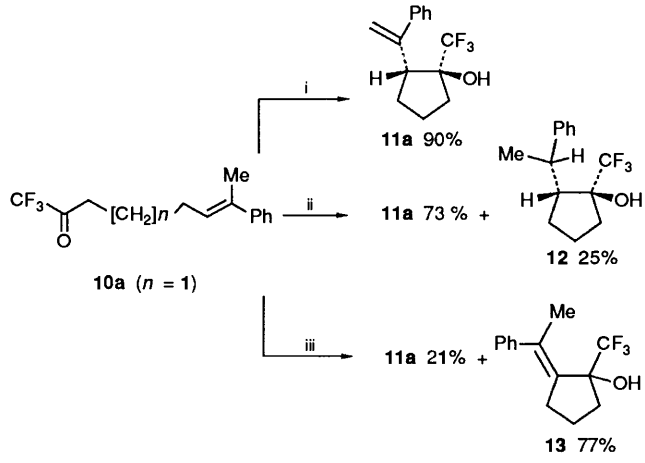


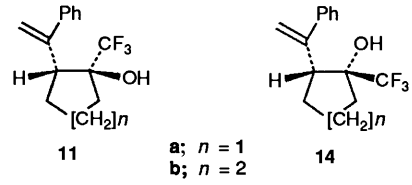
Fig. 1 X-Ray molecular structure of the *p*-nitrobenzoate **7b**



Scheme 3 *Reagent:* $TiCl_4$ or $EtAlCl_2$



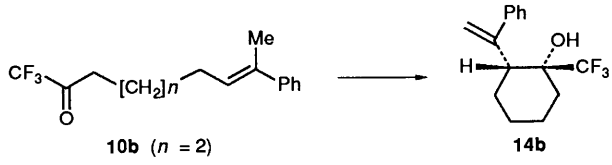
Scheme 4 *Reagents:* i, $MeAlCl_2$; ii, $EtAlCl_2$; iii, $TiCl_4$



From ketone **10a**. The $EtAlCl_2$-initiated cyclization of ketone **10a** (*E*-isomer) provided a mixture of trifluoromethylcyclopentanols **11a** (73%) and **12** (25%) (Scheme 4, Table 2: run 12). Reaction temperature had no influence on this yield ratio. With $TiCl_4$, compound **11a** was the minor product (21%), compound **13** being the major one (77%) (run 14). Reaction with $MeAlCl_2$ provided selectively the styrene **11a** (90%) (run 13). With Me_2AlCl at −80 °C, another isomer, identified as compound **14a** (^{19}F NMR, GC–MS) could be detected but it turned into compound **11a** in the course of the reaction.

Reduction of the styrene **11a** led to compound **12**. Stereochemistry was deduced from NMR data: in compound **12** the presence of a long-range $^6J_{HF}$ coupling (J 0.7 Hz) indicated proximity of the CH_3 and CF_3 groups, only possible in a *cis* configuration.[15] In compound **13**, the presence of both $^6J_{HF}$ and $^5J_{CF}$ coupling is confirmation of the *E*-structure of ethylenic compound.

Formation of Six-membered Rings.—The cyclization of ketone **10b** (*E*-isomer) was found to proceed very selectively with either $EtAlCl_2$ or $TiCl_4$, to afford the cyclohexanol **14b** in very high yield (Scheme 5, Table 2: runs 15 and 16). Only with $EtAlCl_2$ were traces of the other diastereoisomer **11b** be detected by GC. Spectral data did not allow an unambiguous assignment of the stereochemistry to be undertaken.* However, mechanistic considerations and comparison with non-fluorinated series[16] are in favour of a *cis* relationship between the styryl and the hydroxy groups (*vide infra*).



Scheme 5 *Reagent:* Lewis acid

$EtAlCl_2$-induced cyclization of the ketone **15a** afforded the cyclohexenol **16a** (75%), accompanied by small amounts of the cyclohexanol **20** (15%) and traces of dienes **17** (Scheme 6, Table 2: run 17). The position of the double bond in product **16a** was deduced from the deshielding of the methylenic protons at C-2

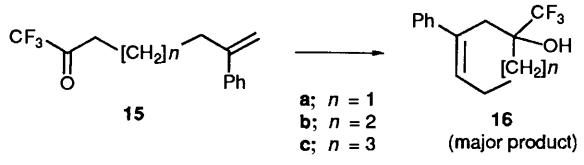
* Attempts to assign stereochemistry in the same way as for five-membered cyclization failed: absence of J_{CF} coupling in the NMR spectrum after reduction of **14b** was not in this case a proof of structure.

Table 2 Cyclization of ketones **10**, **10b**, **15a**, **15b** and **15c**

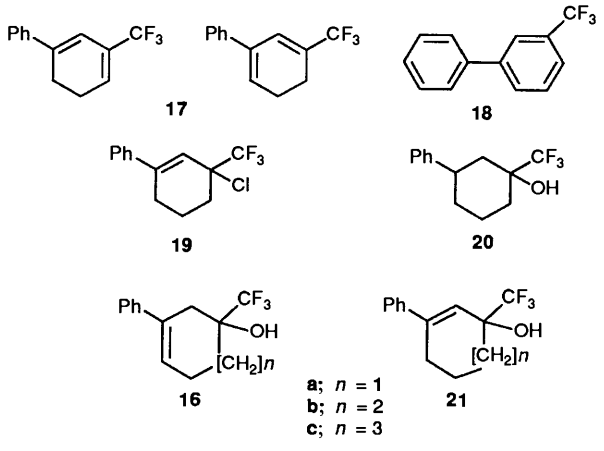
Run	Compound	Lewis acid (mol equiv.)	Temp. (T/°C) and time (t/h)	Products and yields (%)[a]
12	**10a**	$EtAlCl_2$ (1.1)	−78[b] (1)	**11a** 73 (65) **12** 25 (20)
13	**10a**	$MeAlCl_2$ (1.1)	−78 (1)	**11a** 90 (80)
14	**10a**	$TiCl_4$ (1.1)	−78 (0.5)	**11a** 21 (14) **13** 77 (66)
15	**10b**	$EtAlCl_2$ (1.1)	−78[b] (4)	**11b** 3 (0) **14b** 86 (75)
16	**10b**	$TiCl_4$ (1.1)	0 (2)	**14b** (98 (80)
17	**15a**	$EtAlCl_2$ (1.1)	0 (0.5)	**16a** 75 (55) **17** (4) **20** 15(10)
18	**15a**	$TiCl_4$ (1.1)	0 (1.5)	**16a** 65 (51)[c] **17** 25 (15)[c] **19** 6 (0)[c]
19	**15b**	$EtAlCl_2$ (1.5)	−30 (1.5)	**16b** 80 (67)
20	**15c**	$EtAlCl_2$ (1.1)	0 (5)	**14b** 38 (30) **16c** 25 (20)

[a] Estimated yields from GC analysis. Isolated yields are parenthetic values. [b] Same results at −15 °C. [c] When reaction time was extended, products gave the biphenyl **18**.

as well as from the J_{HF} coupling. Similar results were obtained with $TiCl_4$: the cyclohexenol **16a** was the main product (65%) accompanied by dienes **17** (25%) and traces of a by-product that could be the chloride **19** (GC–MS analysis) (run 18). With a longer reaction time, only aromatized product **18** could be isolated.



Scheme 6 *Reagent:* Lewis acid



Formation of Seven- and Eight-membered Rings.—$EtAlCl_2$-promoted cyclization of ketone **15b** was found to provide selectively the cycloheptenol **16b** (80%) (Scheme 6, Table 2: run 19). The position of the double bond was deduced from NMR data.

The ketone **15c** reacted with $EtAlCl_2$ at 0 °C to give the cyclooctenol **16c** (25%) competitively with the cyclohexanol **14b** (38%). This latter is the result of cyclization of the ketone **10b** (*E*-isomer), formed in the reaction medium by isomerization of compound **15c** (run 18). This isomerization is highly dependent on the purity of the Lewis acid. In some experiments isomerization of compound **15b** into **10a** has also been observed.

Discussion

Cyclization of Keto Esters **1** *and* **4**.—Unlike the hydrogenated series,[8] trifluoromethyl β-keto esters are good enophiles and high yields of cyclic products are obtained from substrates **1a**, **1b**, **4a** and **4b**. The stability of the resulting tertiary alcohol–Lewis acid complex, due to the presence of the CF_3 group, allows the use of $TiCl_4$ which seems to be particularly suitable for cyclization of β-keto esters, as already observed in previous results.[4]

From substrates **1a** and **1b**, although allylic hydrogens are available, a type-II ene process is not likely because of a too strained six-membered-ring transition state which would be involved.[6] The presence of an endocyclic double bond in compounds **2a** and **2b** and of different isomers in chlorinated compounds **3**, indicates a non-concerted internal Prins process. The more difficult cyclization of compound **4a** is in agreement with the lower nucleophilicity of the non-substituted double bond in relation to a methallyl group. From substrate **4b**, formation of the indanol **9**, instead of the expected C_5-ring compound **5b** and **6b**, shows the greater nucleophilicity of the phenyl group compared with the vinyl group (Scheme 3).

Complexation of carbonyl groups of ketone and ester groups by a Lewis acid is undoubtedly the root cause of the stereospecificity of the reaction and the *cis* relationship between the hydroxy and ethoxycarbonyl groups.[14] This key role of chelation had already been observed in the cyclization of β-keto esters.[4,8]

Cyclization of Ketones **10a** *and* **10b**.—The cyclization of non-fluorinated carbonyl compounds related to ketone **10a** has been described as being highly dependent on reaction conditions.[6,7,16–18] Both concerted and stepwise ene reactions can occur but the latter process is in most cases favoured, leading to different products *via* a cation intermediate.

The structure and stereochemistry of products from ketone **10a** indicate a two-step process. When the reaction was performed with Me_2AlCl, the ene product **14a** could be detected but its evolution into stereoisomer **11a** is evidence of the reversibility of the ene reaction.[7] With $EtAlCl_2$, the resulting carbocation eliminates to afford product **11a** or traps a hydrogen from the aluminium complex to give compound **12**. Unlike the non-fluorinated series, the ratio of these two products is not dependent on reaction temperature. This reduction is easily avoided with the use of $MeAlCl_2$ as catalyst. No addition of the methyl or ethyl group of the catalyst was observed.

With $TiCl_4$, the carbocation does not trap any chloride but eliminates, mostly to afford the isomeric compound **13**. This different evolution of the intermediate cation in $EtAlCl_2$- and $TiCl_4$-medium has not been elucidated (no isomerization of **11a** to **13** has been observed in the presence of $TiCl_4$, at any temperature).

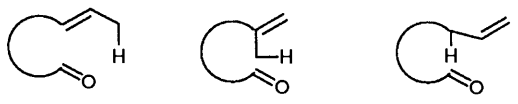


Fig. 2

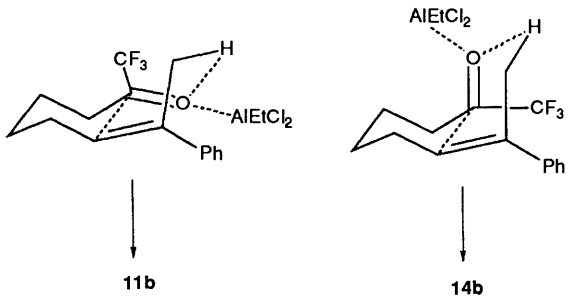


Fig. 3 Transition state of cyclization of compound **10b**

From compound **10b** the absence of any product stemming from a carbocation and the great selectivity of the reaction indicates a concerted type-I ene process (Fig. 2). The exclusive formation of one diastereoisomer is due to geometrical constraints on the transition state. The production of the other isomer, **11b** would imply a twisted *trans*-decalinic structure less favoured than the *cis* chair–chair-like transition leading to compound **14b** (Fig. 3).[19,20] In the ene cyclization of related aldehydes,[7] the stereochemistry of products has been described as depending on the double-bond stereochemistry in the starting material. When the hydrogen implied in the transition state belongs to a methyl group *cis* to the chain, cyclization leads selectively to the products with *cis* hydroxy and styryl groups. All these remarks allowed us to attribute the structure **14b** to the ene product from **10b**.

In this series the process of cyclization of compounds **10a** and **10b** is roughly similar to that of non-fluorinated compounds. The difference lies in greater selectivity of the reaction.

Cyclization of Ketones **15a**, **15b** *and* **15c**.—The structure of starting ketones **15** allows only a type-III ene cyclization process (Fig. 2).[6] This unusual ring formation implies an intermediate sp^2 bridgehead carbon in the transition state. This unfavoured process explains the lack of examples in the literature and particularly for a six-membered-ring formation. Ionic mechanisms seem more likely and, for substrate **15a**, some arguments are in favour of an intermediate cation. Concerted or ionic process can lead to the cyclohexenol **16a**. However, formation of chloride **19** (precursor of **17** and **18**) indicates an intramolecular replacement of OH by Cl, observed only when the C–O bond is weakened, as in allylic and benzylic alkoxides.*[,3b,4] Such an allylic alcohol, compound **21a**, could result either from isomerization of compound **16a** (traces of HCl in $TiCl_4$) or from the deprotonation of a tertiary cation. More striking is the regioselective production of products **16b** and **16c** from substrates **15b** and **15c**, respectively, with no other side-product usually resulting from a cation. In this case, chain length probably diminishes constraints in the transition state and a type-III concerted ene process can be evoked.

Conclusions.—Intramolecular ene carbocyclizations of ω-ethylenic trifluoromethyl carbonyl compounds are a good tool for stereoselective access to functionalized monocycles bearing a CF_3 group. 5, 6, 7-Membered rings were obtained in high yield with different Lewis acids and even an eight-membered-ring cyclization could be achieved by this way.

* In allylic alcohols **2a**, **2b** and **5a**, steric hindrance prevents further nucleophilic substitution as previously noted in the indane series.[4]

Experimental

^1H and ^{19}F NMR spectra were recorded on a Varian EM360 apparatus (60 MHz for ^1H and 56 MHz for ^{19}F) and a Bruker AM300 (300 MHz) for $CDCl_3$ solutions with Me_4Si or $CFCl_3$ as internal standard where appropriate. ^{13}C NMR spectra were determined on a Varian CFT20 (20 MHz) and a Bruker AM300 (75 MHz) for $CDCl_3$ solutions (Me_4Si as internal standard). Reported signal multiplicities are related to C–F coupling. All NMR *J*-values are given in Hz. Mass spectra were obtained on a Normag R10-10 apparatus coupled to a gas-phase chromatograph (capillary column CPSIL-5, 25 m) and a Kratos MS50 spectrometer. Gas chromatographic analysis was performed on a Carlo Erba 4130 chromatograph (capillary column SE30, 10 or 25 m). FT IR spectra were recorded in CCl_4 and in $CHCl_3$ solutions on a Bruker 45 spectrometer. $EtAlCl_2$, as a 1 mol dm^{-3} solution in hexane, and $TiCl_4$ were purchased from Aldrich.

Lewis Acid-facilitated Ketone Cyclization.—Unless otherwise specified, reactions were performed in dry solvents under argon, with reaction volume adjusted to produce a solution 0.04–0.1 mol dm^{-3} in ketone of β-keto ester. Solutions were cooled to the desired temperature and Lewis acid was added dropwise through a septum cap. When starting material had disappeared (followed by GC, after rapid quenching of samples), the mixture was hydrolysed with an equal volume of saturated aq. NH_4Cl, then allowed to attain room temperature. After addition of diethyl ether, the organic layer was washed twice with brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was further purified by column chromatography (SiO_2 60, 70–230 mesh) with (usually) pentane, and then pentane–diethyl ether (95:5), as eluent.

Cyclization of Keto Ester **1a** *with* $EtAlCl_2$.—A solution of the β-keto ester **1a** (0.6 g, 2.1 mmol) in CH_2Cl_2 (50 cm^3) was treated at 0 °C with a 1 mol dm^{-3} solution of $EtAlCl_2$ in hexane (2.3 cm^3, 1.1 mol equiv.) for 3.5 h. Extractive work-up and chromatography afforded *product* **2a** (0.480 g, 80%) (Found: M^+, 280.1289. $C_{13}H_{19}F_3O_3$ requires *M*, 280.1286); δ_H 0.92 (3 H, m), 0.99 (2 H, m), 1.26 (3 H, t, *J* 7), 1.29 (2 H, m), 1.8 (3 H, br s), 2.68 (2 H, q, *J* 16.3), 3.56 (1 H, m, OH), 4.20 (2 H, q, *J* 7) and 5.28 (1 H, m); δ_F −75.6; δ_C 14.0, 14.5, 16.8, 19.6, 35.2, 44.6, 62.2, 61.4, 87.4 (q, ^2J 29, C-1), 122.4, 125.4 (q, ^1J 286, CF_3), 148.7 and 173.7; ν_{max}(FT) ($CHCl_3$)/cm^{-1} 3566, 3485, 3442 (OH), 1718, 1711 and 1674 (CO_2Et); *m/z* 262 (14%, M − 18), 242 (92, M − 38), 215 (65, M − 65), 205 (36, M − 75), 188 (84, M − 92), 141 (100, M − 139) and 109 (68).

Cyclization of Keto Ester **1a** *with* $TiCl_4$.—A solution of compound **1a** (0.4 g, 1.4 mmol) in CH_2Cl_2 (14 cm^3) was treated with $TiCl_4$ (0.17 cm^3, 1.5 mmol) for 3.5 h at 0 °C. Extractive work-up and chromatography yielded the product **2a** (0.300 g, 75%).

Cyclization of Keto Ester **1b** *with* $EtAlCl_2$.—A solution of β-keto ester **1b** (0.4 g, 1.22 mmol) in CH_2Cl_2 (30 cm^3) was treated at 0 °C for 3.5 h with a solution of $EtAlCl_2$ (1 mol dm^{-3} in hexanes; 1.3 cm^3, 1.1 mol equiv.). Extractive work-up and chromatography gave the *product* **2b** (0.320 g, 80%) (Found: M^+, 328.1286. $C_{17}H_{19}F_3O_3$ requires *M*, 328.1284); δ_H 1.11 (3 H, t, *J* 7.2), 1.8 (3 H, br s, Me), 2.7 (2 H, q, ^2J 16), 3.21 (2 H, q, ^2J 14, CH_2Ph), 3.73 (1 H, br s, OH), 4.07 (2 H, q, *J* 7), 5.31 (1 H, s) and 7.2 (5 H, m); δ_F −75.3; δ_C 13.7, 16.9, 38.3, 43.2, 61.6, 62.0, 87.2 (q, ^2J 29, C-1), 122.2, 125.5 (q, ^1J 286, CF_3), 126.8, 128.2, 129.8, 137.1, 148.9 and 173.0; ν_{max}(FT) ($CHCl_3$)/cm^{-1} 3580,

3450, 1726 and 1670; *m/z* 310 (2.5%, M − 18), 290 (19, M − 38), 262 (7, M − 56), 237 (50, M − 91) and 91 (100).

Cyclization of Keto Ester **1b** *with* $TiCl_4$.—A solution of compound **1b** (0.4 g, 1.22 mmol) in CH_2Cl_2 (12 cm^3) was treated at 0 °C with $TiCl_4$ (0.25 g, 1.3 mmol). After 2 h, the usual work-up and chromatography gave compound **2b** (0.360 g, 90%).

Cyclization of Keto Ester **4a** *with* $EtAlCl_2$.—A solution of the keto ester **4a** (0.36 g, 1.35 mmol) in CH_2Cl_2 (34 cm^3) was treated for 7 h at 0 °C with a 1 mol dm^{-3} solution of $EtAlCl_2$ in hexanes (5.4 cm^3, 4 mol equiv.). Extractive work-up and chromatography on SiO_2 gave the mixture (80/20) of products **6a** (0.204 g, 50%), together with compounds **5a** (0.036 g, 10%) and **8** (0.036 g, 10%).

Compound **6a** (*major*). δ_H 0.92 (3 H, t, *J* 7, Me), 1.31 (3 H, t, *J* 7, Me), 1.25–1.45 (3 H, m), 1.87 (1 H, br t), 2.29 (1 H, q, ^2J 15, ^3J 5.5), 2.51 (1 H, q, ^2J 15, ^3J 7.5), 2.88 (1 H, q, ^2J 15, ^3J 7), 2.93 (1 H, q, ^2J 15, ^3J 9), 4.26 (2 H, q, ^3J 7, CH_2O), 4.26 (1 H, sextuplet, CHCl) and 4.6 (1 H, br s, OH); δ_F −75.0; δ_C 13.9, 14.4, 18.8, 34.2, 43.8, 44.7, 52.2, 58.5, 62.0, 83.9 (q, ^2J 29, C-1), 125 (q, ^1J 285, CF_3) and 174.1; ν_{max}(FT) ($CHCl_3$)/cm^{-1} 3575, 3470 (OH), 1720 and 1678 (CO_2Et); *m/z* (CI) 303 (11%, M^+ + 1), 275 (4, M + 2 − 29), 273 (9, M − 29), 257 (21, M − 45), 237 (28), 191 (47), 143 (100) and 115 (62).

Compound **6a** (*minor*). δ_F −74.8; *m/z* 304 (4%, M^+ + 2), 273 (11, M − 29), 257 (7, M − 45), 237 (48), 191 (22), 143 (100) and 115 (67).

Compound **5a** (Found: M^+, 266.1296. $C_{12}H_{17}F_3O_3$ requires *M*, 266.1298); δ_H 0.92 (t, 3 H), 1.2–1.4 (4 H, m), 1.27 (3 H, t), 2.42 (1 H, br d, ^2J 16, ^3J 2.2, 3-H), 3.14 (1 H, br d, ^2J 16, ^3J 2.4, 3-H), 4.24 (2 H, q, ^3J 7), 5.62 (1 H, br d, ^3J 6, ^3J 2.2, 4-H) and 6.19 (1 H, br dd, ^3J 6, ^4J 2.8, $^4J_{HF}$ 1.8, 5-H); δ_F −75.8; δ_C 14.0, 14.5, 19.6, 35.1, 40.8, 60.6, 62.0, 87.3 (q, ^2J 29), 125.2 (q, ^1J 286), 128.9, 137.6 and 173.9; ν_{max}(FT) ($CHCl_3$)/cm^{-1} 3585, 3465 (OH), 1721 and 1677 (CO_2Et); *m/z* 266 (4%, M^+), 246 (43, M − 20), 174 (100, M − 92), 127 (75) and 95 (84).

Compound **8**. δ_H 0.92 (3 H, m), 1.27 (3 H, t, *J* 7), 1.29 (2 H, m), 1.7 (2 H, m), 2.55 (2 H, m), 3.95 (1 H, m), 4.15 (2 H, q, *J* 7) and 5.05–5.75 (3 H, m); δ_F −73.0 (d, *J* 7); *m/z* (CI) 269 (10%, M^+ + 1), 239 (10, M − 29), 226 (28), 177 (25), 169 (92), 157 (88), 141 (90), 95 (83), 67 (71) and 55 (100).

Cyclization of Keto Ester **4a** *with* $TiCl_4$.—A solution of compound **4a** (0.4 g, 1.5 mmol) in CH_2Cl_2 (38 cm^3) was treated at 0 °C with a 1 mol dm^{-3} solution of $TiCl_4$ in CH_2Cl_2 (6 cm^3, 4 mol equiv.). After 26 h, the usual work-up and chromatography gave a mixture of chlorides (85/15) **6a** (0.091 g, 20%) and the cyclopentenol **5a** (0.196 g, 49%).

Cyclization of Keto Ester **4b** *with* $EtAlCl_2$.—A solution of compound **4b** (0.3 g, 0.96 mmol) in CH_2Cl_2 (24 cm^3) was treated at 0 °C for 6 h with a solution of 1 mol dm^{-3} of $EtAlCl_2$ in hexanes (2.9 cm^3, 3 mol equiv.). After extractive work-up and chromatography, the *indanol* **9** was obtained (0.24 g, 80%) (Found: M^+, 314.1129. $C_{16}H_{17}F_3O_3$ requires *M*, 314.1130); δ_H 1.18 (3 H, t, *J* 7), 2.66–2.92 (2 H, m), 3.32 (2 H, q, ^2J 16), 4.13 (2 H, q, *J* 7), 5.1–5.22 (2 H, m), 5.88 (1 H, m) and 7.33 (4 H, m); δ_F −75.5; δ_C 13.6, 37.4, 39.7, 61.5, 61.8, 85.5 (q, ^2J 29, C-1), 118.7, 124.2, 125.2, 125.3 (q, ^1J 287, CF_3), 127.3, 129.9, 139.0, 141.0 and 174.3; *m/z* 296 (79%; M − 18), 276 (16, M − 38), 248 (27), 223 (100, M − 91), 183 (51) and 171 (38).

Cyclization of Keto Ester **4b** *with* $TiCl_4$.—A solution of compound **4b** (0.4 g, 1.3 mmol) in CH_2Cl_2 (13 cm^3) was treated at 0 °C with $TiCl_4$ (0.266 mg, 1.4 mmol). After 3.5 h, extractive work-up and chromatography afforded the product **9** (0.31 g, 77%).

Cyclization of Ketone **10a** *with* $EtAlCl_2$.—A solution of ketone **10a** (0.16 g, 0.6 mmol) in CH_2Cl_2 (12 cm^3) was treated at −78 °C for 1h with a 1 mol dm^{-3} solution of $EtAlCl_2$ in hexanes (0.7 cm^3, 1.1 mol equiv.). After extractive work-up and chromatography on SiO_2, the products **11a** (0.104 g, 65%) and **12** (0.032 g, 20%) were obtained. The same results were obtained when the reaction was performed at −15 °C.

Compound **11a**. (Found: M^+, 256.1075. $C_{14}H_{15}F_3O$ requires *M*, 256.1076); δ_H 2.05 (6 H, m), 2.45 (1 H, br s, OH), 3.35 (1 H, dd, ^3J 11.5, ^3J 7.3, 2-H), 5.34 (1 H, m, ^2J 1, ^4J 0.6, C=CH), 5.58 (1 H, m, ^2J 0.95, ^4J 0.75, C=CH) and 7.32 (5 H, m, Ph); δ_F −79.6; δ_C 21.4, 32.6 and 34.4 (C-3, -4, -5), 48.6 (C-2), 80.1 (q, ^2J 28, C-1), 117.1 (C=CH_2), 126.0 (q, ^1J 287, CF_3), 127.8, 128.3, 128.7, 142.4 (*C*=CH_2) and 147.1; *m/z* 256 (72%, M^+), 239 (47, M − 17), 238 (58, M − 18), 215 (28), 197 (23), 187 (8, M − CF_3), 169 (10), 131 (64), 129 (100, M − 127), 120 (31), 118 (40) and 105 (54).

Compound **12**. δ_H 1.34 (3 H, d of q, ^3J 7, $^6J_{HF}$ 0.7, Me), 1.4–1.7 (5 H, m), 1.9 (1 H, br s, OH), 2.18 (1 H, t, ^3J 8.6), 2.25 (1 H, m, ^3J 7.2, ^3J 7.4, ^3J 10.8, 2-H), 3.09 (1 H, m, ^3J 7.0, ^3J 7.4, *CH*Me) and 7.25 (5 H, m, Ph); δ_F −79.4 (Me); δ_C 21.6, 22.4 (Me,), 29.5, 37.6, 39.1, 49.7, 82.0 (q, ^2J 28, C-1), 126.5, 126.6 (q, ^1J 284, CF_3), 128.0, 128.6 and 145.5; *m/z* 258 (5%, M^+), 115 (5), 106 (22), 105 (100, M − 151) and 91 (9).

Cyclization of Ketone **10a** *with* $MeAlCl_2$.—A solution of ketone **10a** (0.100 g, 0.4 mmol) in CH_2Cl_2 (10 cm^3) was treated at −78 °C for 1 h with a 1 mol dm^{-3} solution of $MeAlCl_2$ in hexanes (0.44 cm^3, 1.1 mol equiv.). After extractive work-up and chromatography on SiO_2, the product **11a** was obtained (0.080 g, 80%).

Cyclization of Ketone **10a** *with* Me_2AlCl.—A solution of ketone **10a** (0.100 g, 0.4 mmol) in CH_2Cl_2 (10 cm^3) was treated at −78 °C for 1 h with a 1 mol dm^{-3} solution of Me_2AlCl in hexanes (0.44 cm^3, 1.1 mol equiv.). At the beginning of the reaction compound **14a** could be detected, in addition to **11a**. After extractive work-up and chromatography on SiO_2, compound **11a** was the only product obtained (0.080 g, 80%).

Compound **14a**. δ_F −79.0; *m/z* 256 (29%, M^+), 187 (4, M − CF_3), 145 (34), 144 (80), 131 (78), 130 (52), 129 (100), 116 (25), 105 (14) and 91 (67).

Cyclization of Ketone **10a** *with* $TiCl_4$.—A solution of ketone **10a** (0.100 g, 0.4 mmol) in CH_2Cl_2 (10 cm^3) was treated at −78 °C for 0.5 h with a 1 mol dm^{-3} solution of $TiCl_4$ in CH_2Cl_2 (0.44 cm^3, 1.1 mol equiv.). After extractive work-up and chromatography on SiO_2, the products **11a** (0.014 g, 14%), **14a** (traces) and **13** (0.066 mg, 66%) were obtained.

Compound **14a**. δ_H (*inter alia*) 5.20 (1 H, d, ^2J 1.2, C=CH) and 5.56 (1 H, d, ^2J 1.2, C=CH); *m/z* 256 (20%, M^+), 187 (9, M − CF_3), 144 (78), 129 (100), 115 (12), 105 (29), 91 (67) and 69 (29).

Compound **13**. δ_H 1.45 (2 H, m), 1.7 (1 H, m), 2.10 (q, $^6J_{HF}$ 1.2, Me), 2.30 (4 H, m) and 7.2 (5 H, m, Ph); δ_F −78.2 (s); δ_C 20.9 (q, $^5J_{CF}$ 3.5, Me), 21.6, 33.8, 39.0, 81.4 (q, ^2J 29.7, C-1), 126.4 (q, ^1J 285, CF_3), 126.5, 126.9, 128.0, 134.5 and 138.2 (C=C) and 145.0; *m/z* 256 (28%, M^+), 238 (6, M − 18), 188 (53), 187 (100, M − CF_3), 169 (18), 129 (16), 115 (14) and 91 (9).

Reduction of Compound **11a**.—A solution of compound **11a** (0.1 g, 0.4 mmol) in methanol (20 cm^3) was stirred in a Parr apparatus, in the presence of 5% Pd/C (30 mg), at room temperature for 14 h under hydrogen. After filtration of the catalyst, the filtrate was evaporated under reduced pressure and the crude product was chromatographed on silica gel to give compound **12** (90 mg, 90%).

Cyclization of Ketone **10b** *with* $EtAlCl_2$.—A solution of ketone **10b** (0.5 g, 1.85 mmol) in CH_2Cl_2 (45 cm^3) was treated with a 1

mol dm^{-3} solution of $EtAlCl_2$ in hexanes (2 cm^3, 1 mol equiv.) at −78 °C for 4 h. The reaction was carried out and the product worked up according to the general procedure. The product **14b** was isolated (0.375 g, 75%). Traces of the isomer **11b** were detected by GC.

Compound **14b** (Found: M^+, 270.1235. $C_{15}H_{17}F_3O$ requires *M*, 270.1231); δ_H 1.3–2.05 (8 H, m), 2.48 (1 H, br s, OH), 2.98 (1 H, dd, ^3J 12, ^3J 4), 5.27 (1 H, s), 5.36 (1 H, s) and 7.32 (5 H, m); δ_F −80.0; δ_C 20.0, 25.8, 30.1, 30.9, 44.6, 73.9 (q, ^2J 27, C-1), 115.5, 125.9 (q, ^1J 287, CF_3), 127.5, 128.1, 142.7 and 150.6; *m/z* 270 (45%, M^+), 255 (14, M − 15), 237 (64), 215 (30), 197 (18), 143 (44), 131 (30), 129 (45), 128 (34), 120 (33), 118 (75), 117 (34), 115 (50), 105 (35), 103 (40), 91 (100), 78 (30), 77 (66), 55 (21) and 51 (20).

Compound **11b**. *m/z* 270 (33%), 255 (14), 237 (63), 215 (37), 197 (24), 143 (61), 131 (27), 129 (60), 128 (45), 120 (5), 118 (100), 117 (44), 115 (57), 105 (42), 103 (51), 91 (94), 78 (35), 77 (73), 55 (21) and 51 (24).

Cyclization of Ketone **10b** *with* $TiCl_4$.—A solution of ketone **10b** (0.130 g, 0.48 mmol) in CH_2Cl_2 (5 cm^3) was treated with $TiCl_4$ (0.52 cm^3 of a 1 mol dm^{-3} solution in CH_2Cl_2, 1.1 mol equiv.), at 0 °C for 2 h. After usual work-up and chromatography, the product **14b** was isolated (0.112 g, 80%).

Cyclization of Ketone **15a** *with* $EtAlCl_2$.—A solution of ketone **15a** (0.3 g, 1.24 mmol) in CH_2Cl_2 (30 cm^3) was treated with a 1 mol dm^{-3} solution of $EtAlCl_2$ in hexanes (1.36 cm^3, 1.1 mol equiv.) at 0 °C for 0.5 h. After work-up and chromatography, the products **16a** (0.165 g, 55%) and **20** (30 mg, 10%) were isolated.

Compound **16a**. (Found: M^+, 242.0918. $C_{13}H_{13}F_3O$ requires *M*, 242.0919); δ_H 1.88 (2 H, m), 2.25 (2 H, m), 2.55 (1 H, d, ^2J 18, 2-H), 2.80 (1 H, q, ^2J 18, $^4J_{HF}$ 2, 2-H), 6.15 (1 H, m) and 7.32 (5 H, m); δ_F −84.8; δ_C 21.2, 25.5, 33.2, 72.3 (q, ^2J 29, C-1), 123.4, 125.1, 126.3 (q, ^1J 284, CF_3), 127.3, 128.4, 131.8 and 140.9; *m/z* 242 (34%, M^+), 225 (21, M − H_2O), 183 (7, M − CF_3), 155 (100, M − CF_3 − H_2O), 129 (24), 115 (22) and 91 (23).

Compound **20**. δ_F −85.5; *m/z* 244 (7%, M^+), 226 (94, M − 18), 157 (100), 129 (28), 115 (17), 91 (59) and 77 (16).

Cyclization of Ketone **15a** *with* $TiCl_4$.—A solution of ketone **15a** (0.26 g, 1.02 mmol) in CH_2Cl_2 (27 cm^3) was treated with a 1 mol dm^{-3} solution of $TiCl_4$ in CH_2Cl_2 (1.2 cm^3, 1.1 mol equiv.) at 0 °C for 1.5 h. Work-up and chromatography gave the dienes **17** (33 mg, 15%), the cyclohexenol **16a** (133 mg, 51%) and the chloride **19** (detected by GC–MS).

Compound **17**. δ_F −69.8; *m/z* 224 (67%, M^+), 183 (29), 115 (100), 154 (97), 126 (30), 114 (28), 91 (26) and 77 (36).

Compound **19**. δ_F −79.3; *m/z* 262 and 260 (11%, M^+), 225 (89, M − Cl), 224 (36, M − HCl), 183 (22), 177 (10), 155 (80), 91 (100) and 77 (46).

When reaction time was extended to 5 h, a complex mixture was obtained from which was isolated the biphenyl **18** (0.066 g, 25%); δ_F −63.5; *m/z* 222 (100%, M^+) and 152 (24).

Cyclization of Ketone **15b** *with* $EtAlCl_2$.—A solution of ketone **15b** (200 mg, 0.78 mmol) in CH_2Cl_2 (20 cm^3) was treated by a 1 mol dm^{-3} solution of $EtAlCl_2$ in hexanes (1.17 cm^3, 1.5 mol equiv.) at −30 °C for 1.5 h. The reaction was carried out and the product was worked up according to the general procedure. After chromatography of the crude product (190 mg), the *cycloheptenol* **16b** was isolated (135 mg, 67%) (Found: M^+, 256.1076. $C_{14}H_{15}F_3O$ requires *M*, 256.1075); δ_H 1.25–2.40 (6 H, m), 3.02 (2 H, q, ^2J 15), 6.36 (1 H, br t, *J* 6) and 7.33 (5 H, m); δ_F −84.5; δ_C 19.9, 28.1, 35.9, 36.1, 72.0 (q, ^2J 27, C-1), 126.2, 126.6 (q, ^1J 285, CF_3), 127.1, 128.5, 132.4, 136.5 and 143.6; *m/z* 256 (53%; M^+), 238 (42, M − H_2O), 210 (59), 169 (64) and 129 (100).

Cyclization of Ketone **15c** *with* $EtAlCl_2$.—A solution of the ketone **15c** (0.5 g, 1.85 mmol) in CH_2Cl_2 (45 cm^3) was treated with a 1 mol dm^{-3} solution of $EtAlCl_2$ in hexanes (2.04 cm^3) at 0 °C for 5 h. After work-up and chromatography, the cyclohexanol **14b** (0.150 g, 30%) and then the cyclooctenol **16c** (0.100 g, 20%) were isolated.

Compound **16c**. δ_H 1.3–2.3 (8 H, m), 2.98 (2 H, q, ^2J 15), 6.10 (1 H, m) and 7.30 (5 H, m); δ_F −82.6; δ_C 19.4, 27.2, 28.9, 32.0, 33.1, 77.2 (q, ^2J 26, C-1), 126.3, 126.5 (q, ^1J 286, CF_3), 127.1, 127.8, 128.5, 131.4 and 141.0.

*Mono-*p*-nitrobenzoate* **7b** *of Diol* **7a**.—$LiAlH_4$ (0.18 g, 4.7 mmol) was added to a solution of compound **2b** (1.41 g, 4.3 mmol) in Et_2O (50 cm^3) at room temperature. The reaction mixture was refluxed for 2.5 h. Hydrolysis and work-up gave the diol **7a** (1.16 g, 85%); δ_H 1.73 (3 H, br s), 2.7–3.5 (6 H, m), 3.48 (2 H, q, CH_2OH), 4.6 (m, OH), 5.3 (1 H, br s) and 7.26 (5 H, s); δ_F −76.2.

p-Nitrobenzoyl chloride (1.22 g, 6.6 mmol) was added to a solution of this crude product (1.15 g, 3.6 mmol) in CH_2Cl_2 (15 cm^3) in the presence of pyridine (0.58 g, 7.2 mmol) and 4-(dimethylamino)pyridine (0.1 g). After 24 h at room temperature, and 3 h at reflux, the reaction mixture was treated with 2 mol dm^{-3} HCl and then extracted with Et_2O. The organic layer was washed successively twice with 1 mol dm^{-3} HCl, saturated aq. $NaHCO_3$, and brine, dried over Na_2SO_4, and evaporated to give a crude product, which was purified on SiO_2 [hexane–CH_2Cl_2 (1:1)]. The nitrobenzoate **7b** was isolated as crystals from Et_2O–hexane, m.p. 104 °C; δ_H 1.82 (3 H, br s), 2.5–3.5 (6 H, m), 4.4 (q, ^2J 12), 5.41 (1 H, m), 7.22 (5 H, s) and 8.15 (4 H, m); δ_F −74.8.

Crystal Data.—Crystal of dimensions 0.6 × 0.4 × 0.4 mm. Graphite-monochromated 4-circle Phillips diffractometer; wave length Mo*K*α 0.7107 Å $\theta/2\theta$ scan, θ range 2–28°, speed 0.04° s^{-1}, width 1.2°, background twice 15 s. Three standards every 3 h decay less than 6% corrected, as also L_p; $\mu < 2$ cm^{-1}. Space group *P*1, *Z* = 2, *a* = 9.955(5), *b* = 10.697(6), *c* = 11.158(6) Å, α = 100.71(7), β = 95.79(6), γ = 115.06(6)°. *V* = 1035 $Å^3$. From 4860 measured data, 3106 > 3σ(*I*) were used.

Direct methods [21] and large blocks least-squares [22] were used. All H-atoms were located by difference synthesis, and refined with constraints. Anisotropic thermal parameters were refined to C, N, O and F atoms. Final weighting scheme $w = [\sigma(F)^2 + 0.009F^2]^{-1}$. Final conventional *R*-factor 4.9%.*

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* *Supplementary data* (see Instructions for Authors, issue 1). Bond distances and angles are available from the Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge, UK.

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