isolated yield by method C from 42.93 g (0.271 mol) of **1a** and 31.33 g (0.359 mol) of *tert*-amylamine in 50 mL of toluene. ^{1}H NMR: δ 0.76 (t, J = 7.45 Hz, 3 H), 1.21 (s, 6 H), 1.62 (q, J = 7.45 Hz, 2 H), 2.18 (s, 3 H), 3.26 (s, 2 H), 6.69 (br s, 1 H, NH). ^{13}C NMR: δ 7.96 (CH_3), 25.99 (2 C, CH_3), 30.72 (CH_3), 32.57 (CH_2), 50.72 (CH_2), 53.96 (C), 164.70, 205.49. IR: 3340, 3080, 2980, 2940, 2890, 1730, 1665, 1560, 1468, 1420, 1370, 1340, 1208, 1169 cm^{-1}. EI-MS: m/z (rel int) 171 (1), 156 (3), 142 (35), 72 (43), 58 (100), 43 (43). HRMS: 171.1260 (calcd for $C_9H_{17}NO_2$ 171.1259).

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Supplementary Material Available: A listing of additional spectral data for compounds **6**, **8–12**, **14**, and **15** as well as ^{1}H and ^{13}C spectra for compounds **5**, **16**, **23**, **24**, and **25** (12 pages). Ordering information is given on any current masthead page.

Construction of Trifluoromethylated Quarternary Carbons via Diels–Alder Reactions of 2-(Trifluoromethyl)propenoic Acid Derivatives: Application to the Synthesis of 16,16,16-Trifluororetinal[1]

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Diels–Alder reactions of 2-(trifluoromethyl)propenoic acid (**1**) and its 2,2,2-trifluoroethyl ester **2** with various dienes gave adducts in good yields. In Lewis acid catalyzed Diels–Alder reactions of **2**, the combination of the Lewis acid and solvent proved to be crucial. For example, polymerization occurred in the case of $TiCl_4$–CH_2Cl_2 and adduct formation was observed with $TiCl_4$–toluene and $TiCl_2$(O-*i*-Pr)$_2$–CH_2Cl_2. In the $TiCl_4$-catalyzed Diels–Alder reaction of the 2-(trifluoromethyl)propenoate ester **3** of D-pantolactone with butadiene, the formation of the *R* configurational quaternary carbon bearing the trifluoromethyl group was confirmed by X-ray crystallographic analysis of the adduct **20**. No polymerization of ester **3** could be detected in the presence of $TiCl_4$ in CH_2Cl_2. The reactivity difference between **2** and **3** in $TiCl_4$-catalyzed Diels–Alder reactions may possibly be attributable to the stabilization of the **3**–$TiCl_4$ complex or weakening of Lewis acidity by coordination of the bidentate ester group of **3**. The synthesis of *all-trans*-16,16,16-trifluororetinal (**4**), which is considered to be an important analogue for the study of retinal-binding protein, was conducted on the basis of these results. Comparison of the absorption maximum (362 nm) of **4** with other trifluororetinals **34** (362 nm) and **35** (382 nm) reported previously suggests the possibility of a large torsion of the conjugated system between the ring and the polyenal side chain in **4**.

Introduction

The introduction of fluoro substituents into biochemically important molecules has attracted much attention in organic, biological, and medicinal chemistry for studying the biochemical process of the parent molecule and/or enhanced or altered activity of the fluoro analogue.[2] For this purpose, new and/or more effective methods for the selective introduction of fluoro substituents into organic molecules should be developed. The growing number of fluorinated compounds, commercially available, should serve as starting materials for preparing functionalized fluoro molecules. It is also interesting to compare the reactivity of the fluorinated molecule with the related hydrocarbon during reactions. In recent examinations of the reactivity of fluorinated compounds, the electronic effect of the fluoroalkyl group had been found to considerably affect the stereochemical results in the asymmetric reduction of fluoroalkyl ketones with binaphthol-mediated aluminum hydride reagent,[3] in nucleophilic attack on trifluoromethylated cyclohexanone derivatives,[4] in the α-hydroxylation of the enolate prepared from γ,γ,γ-trifluoroester derivative,[5] and in Pd(0)-mediated intramolecular lactonization.[6] We describe herein the results of Diels–Alder reactions of 2-(trifluoromethyl)propenoic acid (**1**) and esters **2** and **3** for construction of quaternary carbons bearing a trifluoromethyl group and the preparation of 16,16,16-trifluororetinal (**4**).[7]

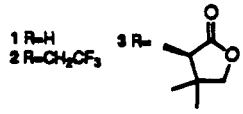
Results and Discussion

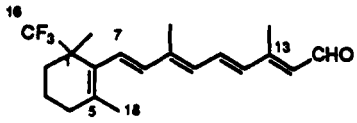
2-(Trifluoromethyl)propenoic acid (**1**) and its derivatives are strong acceptors in the Michael reaction and have been utilized in the synthesis of the fluoro analogues of nucleoside bases and amino acid derivatives.[8] The cyclo-

(1) Preliminary communication: Hanzawa, Y.; Suzuki, M.; Kobayashi, Y. *Tetrahedron Lett.* **1989**, *30*, 571.
(2) (a) Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha, Ltd., and Elsevier Biomedical Press: Amsterdam, 1982. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.
(3) Hanzawa, Y.; Kawagoe, K.; Kobayashi, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2609.
(4) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.
(5) Morizawa, Y.; Yasuda, A.; Uchida, K. *Tetrahedron Lett.* **1986**, *27*, 1833.
(6) Hanzawa, Y.; Ishizawa, S.; Ito, H.; Kobayashi, Y.; Taguchi, T. *J. Chem. Soc., Chem. Commun.* **1990**, 394.
(7) Numbering of the retinoids system was used.

0022-3263/91/1956-1718$02.50/0

addition of 1 with diazomethane has been reported to give a 1,3-dipolar cycloadduct.[9] Although 1 and its esters are expected to be good dienophiles owing to the electronegative trifluoromethyl and carbonyl functions,[10] to the best of our knowledge, there are no reports on their Diels–Alder reactivity.





4

Initially, we examined the Diels–Alder reactivity of 1 with typical dienes. Reaction with cyclopentadiene proceeded instantaneously at room temperature to give a mixture of stereoisomers **5a** and **5b** (2:1 ratio) (Scheme I). The stereochemistry of the adduct **5** was determined by iodo lactonization of the crude reaction mixture (I_2–KI, $NaHCO_3$), in which only endo carboxylic acid **5a** was cyclized to give iodo lactone **7**. It should be noted that the ratio (endo-COOH/exo-COOH = 2) of the cyclopentadiene adduct **5** was the inverse of that obtained in reactions of α-alkylated propenoic acids with cyclopentadiene,[11] which give the exo-COOH product preferentially. Considering the steric size of the trifluoromethyl group being similar to that of an isopropyl group,[12] the pseudo π-character or the electronic effect of the trifluoromethyl group may possibly affect the approach of the dienophile.[13] Similar results have also have been observed in Diels–Alder reactions of 3-(trifluoromethyl)propenoic acid and 3,3,3-trifluoro-1-(phenylsulfonyl)propene.[14]

Adducts were also obtained in good yields with acyclic dienes at higher temperature (110–120 °C, sealed tube). Regiochemistry of the isoprene adduct **8** favored the para isomer **8a** (para/meta = 10/1). The structure of the major isomer of **8a** was confirmed by IR and ^{13}C NMR spectra of the lactone **13** obtained by treating a mixture of **8a** and **8b** with iodine in basic media followed by the reduction (nBu_3SnH, AIBN) of iodide **11**. In the IR and ^{13}C NMR spectra of **13**, a typical δ-lactone carbonyl absorption (ν 1750 cm^{-1}) and seven ^{13}C NMR signals at 23.5, 25, 30, 46, 82, 125, and 169 ppm indicated the lactone **13** to have a symmetry plane, which would not be present in the product from the minor iodo lactone **12**.[15] The reaction of 2,4-pentadien-1-ol[16] with **1** gave volatile lactone **14** (48%). An attempted intramolecular Diels–Alder reaction of **15** prepared by reaction of 2-(trifluoromethyl)propenoyl chloride[17] with 2,4-pentadien-1-ol failed to produce the cycloadduct. It is thus evident that lactone **14** is formed through an intermolecular Diels–Alder reaction of 2,4-pentadien-1-ol[16] with **1** and subsequent lactonization.

Reaction of ester **2**[18] with *trans*-1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (Danishefsky's diene)[19] proceeded exothermically at 0 °C to give a crude primary product, which was converted directly to enone **17** with acid (TsOH/MeOH) in 78% yield. Attempts to effect the Diels–Alder reaction of **2** with isoprene by Lewis acid catalysis resulted in extensive polymerization in the $TiCl_4/CH_2Cl_2$ system (Table I). Although polymerization was prevented by $TiCl_4$ in toluene or $TiCl_2(O\text{-}i\text{-}Pr)_2$[20] in CH_2Cl_2, only moderate yields of **9** were obtained. The relation between the acidity of the Lewis acid and basicity of the solvent is important for successful Diels–Alder reactions of **2**. It should be noted that the regiochemical

Table I. Diels–Alder Reactions of 2 with Isoprene with and without Lewis Acid Catalysts

ratio (2/isoprene)	Lewis acid (equiv)	solvent	yield (%)[a] of **9**	reactn temp (°C)
1/1.1	none	CH_2Cl_2	92	120
1/1.1	$EtAlCl_2$ (0.8)	CH_2Cl_2	51	−20
1/3	$TiCl_4$ (0.10)	CH_2Cl_2	polymrzn	−20
1/3	$TiCl_4$ (0.13)	toluene	38	0
1/30	$TiCl_2(O\text{-}i\text{-}Pr)_2$ (1.0)	CH_2Cl_2	54	0–25
1/3.6	$BF_3{\cdot}OEt_2$ (0.8)	CH_2Cl_2	polymrzn	0

[a] The ratio of the regioisomer (para isomer/meta isomer); ≥95%.

Table II. Lewis Acids in Diels–Alder Reactions of 3 with Isoprene[a]

Lewis acid[b]	yield (%) of **10**	diastereomeric ratio[c]	reactn condtns	
			temp (°C)	time (h)
$TiCl_4$	80	2/98	−23	
$ZrCl_4$	94	6/92	−23	
$EtAlCl_2$	67	40/55	−23	2
Et_2AlCl	65	22/32	−23	2
$BF_3{\cdot}OEt_2$	polymrzn		−23	
$SnCl_4$	recvry of **3**		−23–rt	24

[a] The reaction was carried out in CH_2Cl_2/hexane 7/1 (**3**, 1 mmol/20 mL). No detectable amount of the meta isomer of **10** was observed. [b] An equimolar amount of Lewis acid to **3** was used. [c] Determined by GLC and NMR (^1H and ^{19}F).

Table III. Diels–Alder Reactions of 3 with Dienes at −23 °C

diene	Lewis acid[a]	yield (%)	diastereomeric excess	product
cyclopentadiene	$TiCl_4$	95[b]	98[c]	**6a** (endo-COOR)
butadiene	$TiCl_4$	86	98[c]	**20**
isoprene	$TiCl_4$	80	96[c]	**10**
16	$TiCl_4$	81	45[d]	**19**
16	$ZrCl_4$	70	57	

[a] 0.13 equiv of Lewis acid to **3** (1 mmol/1 mL of CH_2Cl_2) was used. [b] The ratio of endo/exo = 8. [c] Determined by GLC and NMR (^1H and ^{19}F). [d] See ref 23.

(8) (a) Fuchikami, T.; Ojima, I. *Tetrahedron Lett.* **1982**, *23*, 4099. (b) Fuchikami, T.; Yamanouchi, A.; Ojima, I. *Synthesis* **1984**, 766. (c) Kitazume, T.; Ohnogi, T. *Ibid.* **1988**, 614. (d) Ojima, I.; Kato, K.; Nakahashi, K. *J. Org. Chem.* **1989**, *54*, 4511. (e) Ymazaki, T.; Ohnogi, T.; Kitazume, T. *Tetrahedron: Asymmetry* **1990**, *1*, 215.

(9) Fuchikami, T.; Shibata, Y.; Suzuki, Y. *Tetrahedron Lett.* **1986**, *27*, 3173.

(10) Diels–Alder reaction of 3,3,3-trifluoropropene: (a) Ojima, I.; Yatabe, M.; Funcikami, T. *J. Org. Chem.* **1986**, *47*, 2051. (b) Gaede, B.; Balthazor, T. M. *Ibid.* **1983**, *48*, 276.

(11) (a) Meek, J. S.; Trapp, W. B. *J. Am. Chem. Soc.* **1957**, *79*, 3909. (b) Martin, J. G.; Hill, R. K. *Chem. Rev.* **1961**, *61*, 537.

(12) Bott, G. *J. Am. Chem. Soc.* **1980**, *102*, 618.

(13) Bamgardner, C. L.; Bunch, J. E.; Whangbo, M.-H. *Tetrahedron Lett.* **1986**, *27*, 1883 and references cited therein.

(14) (a) McBee, E. T.; Keogh, M. J.; Levek, R. P.; Weseler, E. P. *J. Org. Chem.* **1983**, *38*, 632. (b) Taguchi, T.; Hosoda, A.; Tomizawa, G.; Kawara, A.; Masuo, T.; Suda, Y.; Nakajima, M.; Kobayashi, Y. *Chem. Pharm. Bull.* **1987**, *35*, 909.

(15) In the iodo lactonization of the mixture of the isoprene adduct **8**, δ-lactone and γ-lactone were obtained from the major **8a** (para isomer) and minor **8b** (meta isomer) adducts, respectively.

(16) White, J. D.; Sheldon, B. G. *J. Org. Chem.* **1981**, *46*, 2273.

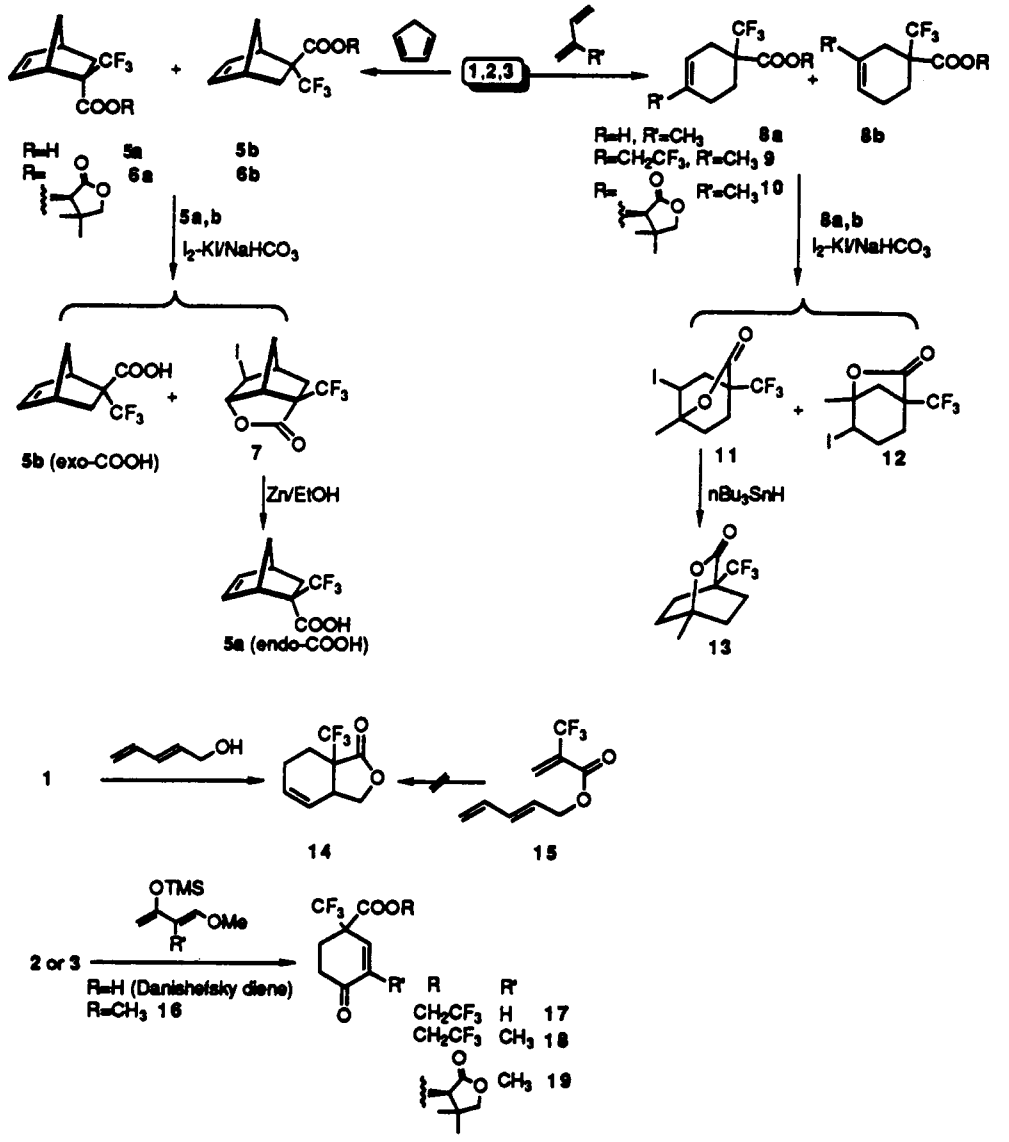
(17) Prepared by the reaction of **1** with phthaloyl dichloride in a good yield.

(18) *Jpn Kokai Tokkyo Koho*, JP 60 42,252; *Chem. Abstr.* **1985**, *103*, 141472n.

(19) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

(20) Mukaiyama, T.; Ishida, A. *Chem. Lett.* **1975**, 319.

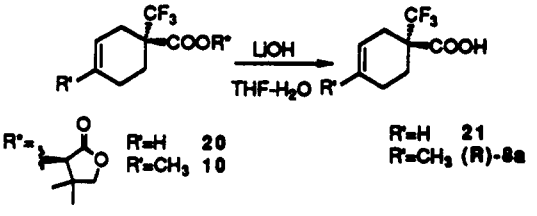
Scheme I



preference of 2 was greatly enhanced (Table I).

Diastereoselective Diels–Alder Reactions. Diastereoselective Diels–Alder reaction[21] of 2-(trifluoromethyl)propenoate ester 3 of D-pantolactone, the use of which as a chiral auxiliary has been developed by Helmchen,[22] was examined. The synthesis of 3 was carried out in 85% yield by treating 2-(trifluoromethyl)propenoyl chloride[17] with D-pantolactone, commercially available in optically pure form. Among the Lewis acids examined in the reactions of 3 with isoprene in CH_2Cl_2 at −23 °C, $TiCl_4$ and $ZrCl_4$ showed excellent diastereoselection (Table II). However, with $EtAlCl_2$ and Et_2AlCl, poor diastereoselection, extensive polymerization (BF_3·Et_2O), or recovery of 3 ($SnCl_4$) was observed. It should be noted that ester 2 was polymerized easily with $TiCl_4$ in CH_2Cl_2 whereas no polymerization occurred with 3. Under $TiCl_4$-catalyzed conditions, the reason for the excellent reactivity of 3 without polymerization of the dienophile may possibly have been the bidentate ester group of 3, which coordinates to the central Ti atom to stabilize the complex, as shown in Figure 2.

Scheme II



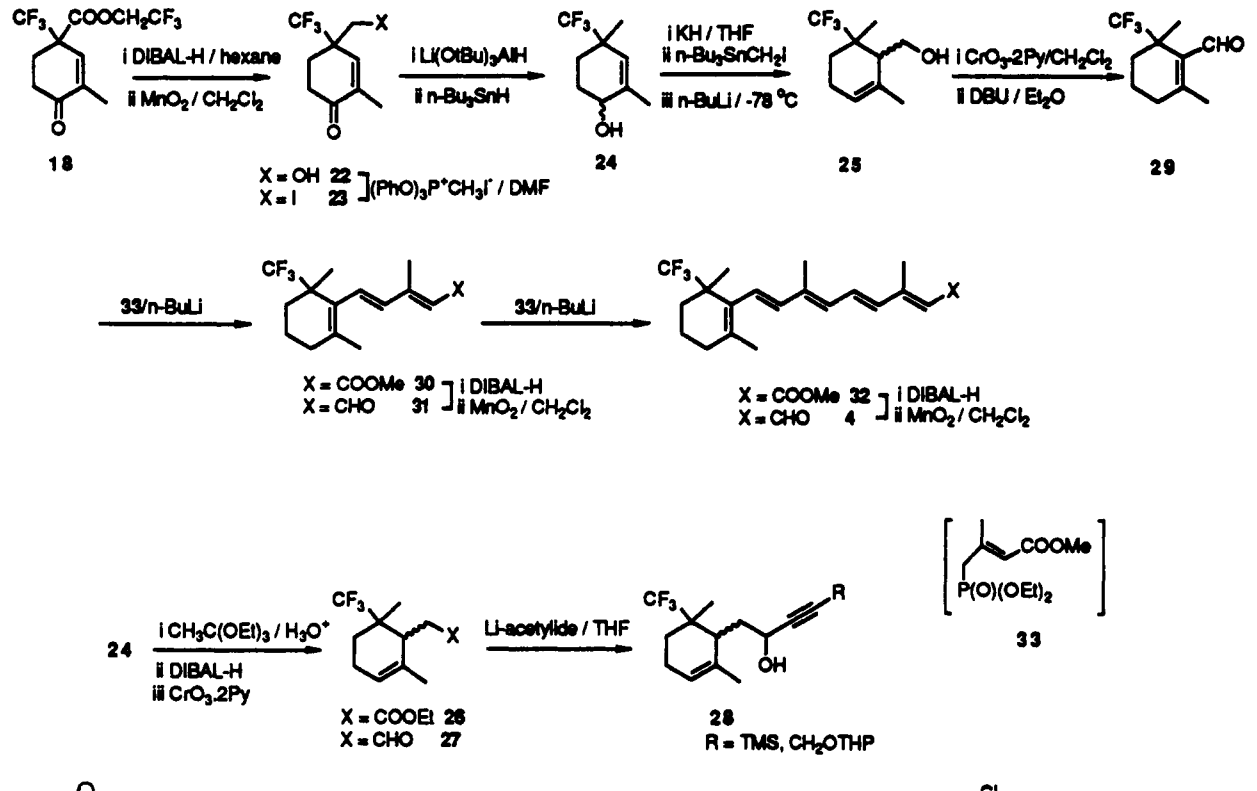
Results of the $TiCl_4$- or $ZrCl_4$-catalyzed Diels–Alder reactions of 3 with several dienes are shown in Table III.[23] The adducts were purified by recrystallization to give diastereomerically pure compounds and subsequent hydrolysis (LiOH/THF–H_2O) (Scheme II) of the adducts gave enantiomerically pure carboxylic acids in good yields except in the case of adduct 19. An attempt to obtain a better diastereomeric excess in the reaction of 3 with 1-methoxy-2-methyl-3-(trimethylsiloxy)-1,3-butadiene (16)[24]

(21) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* 1988, *110*, 1238 and the references cited therein.

(22) Poll, T.; Sobczak, A.; Hartman, H.; Helmchen, G. *Tetrahedron Lett.* 1985, *26*, 3095.

(23) Diastereomeric excess was determined by GLC (OV-101 25 m) and ^1H NMR (400 MHz) except in the case of the adduct 19 obtained from 16. Its optical purity was determined by measuring the ^1H and ^{19}F NMR signals of the (*S*)-*O*-acetylmandelic acid ester of the enone alcohol 22 (optically active), which was obtained in four steps from the crude adduct 19 [(i) TsOH/MeOH, (ii) DIBAL-H, (iii) MnO_2, (iv) (*S*)-*O*-acetylmandelic acid/DCC].

Scheme III



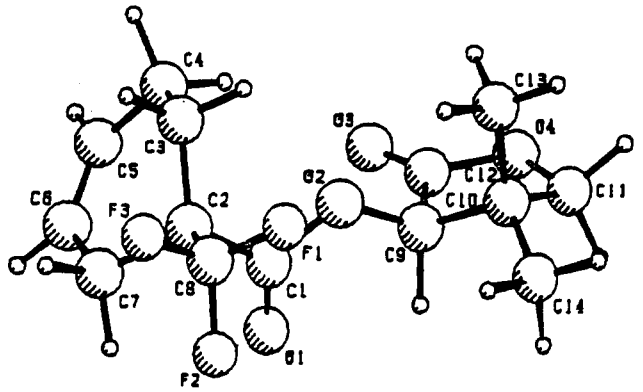


Figure 1. Computer-generated perspective drawing of **20** obtained by X-ray analysis.

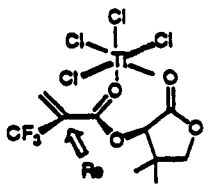


Figure 2. Syn-planar conformation of $TiCl_4$-complexed **3**.

at lower temperature (−78 °C) failed to yield adduct **19**. The absolute configuration at the trifluoromethylated chiral center of the butadiene adduct **20** ($[\alpha]_D$ 26.4° (*c* 0.86, $CHCl_3$)) was determined to be the *R* configuration by X-ray analysis (Figure 1).[25] Configurations at the trifluoromethylated quaternary carbons in the other adducts were inferred by analogy with the X-ray result for adduct **20**. The diastereoselectivity can be explained by analogy with a model proposed by Helmchen:[22] the *si* face of the syn-planar dienophile is shielded by one of the chlorine atoms of the chelating $TiCl_4$ and the *re* face of the dienophile becomes the preferred site for attack. It is of interest that the trifluoromethyl substituent of **3**, an electronegative and sterically demanding group,[12] did not change the syn-planar conformation of the chelated dienophile established for the nonsubstituted acrylate system[22] (Figure 2).

Synthesis of 16,16,16-Trifluororetinal (4).[7] Studies have been conducted on the synthesis and biochemical aspects of fluoro analogues of retinal to obtain data on the well-known retinal-binding proteins[26] bacteriorhodopsin (bR) and rhodopsin (Rh). In both proteins, the retinal molecule is bound to the ω-amino group of lysine in the form of a protonated Schiff base. Regarding the binding sites for the reginal chromophore in both proteins, it has been speculated that an electronic charge due to the amino acid residue at particular positions near the retinal chromophore may possibly cause the bathochromic shift of the absorption maximum to a greater extent than that of the protonated Schiff base of retinal with *n*-butylamine.[27] The electronic characteristics of fluorine in 18,18,18-trifluororetinal (**34**)[7,26a] have provided support for a position of negative electronic charge within the retinal-binding site of bR and the unique character of fluoro-bR.[26] For the

(24) Danishefsky, S.; Yan, C. F.; Singh, R. K.; Gammill, R. B.; McMcurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

(25) Crystals for X-ray analysis were prepared by recrystallization from hexane–EtOAc. A total of 1367 reflections out of 1780 within the 2θ range of 6° through 156° were collected on a Philips PW1100 diffractometere using Cu Kα radiation (λ = 1.541 78 Å). Crystal data of **20**: mol formula = $C_{14}H_{17}O_4F_3$, M_r = 306.3, monoclinic, space group $P2_1$, *a* = 11.487 (6) Å, *b* = 6.317 (4) Å, *c* = 10.731 (6) Å, β = 96.42 (5)°, *V* = 774 Å^3, *Z* = 2, D_x = 1.314 g cm^{-1}. The final *R* factor was 0.056.

(26) (a) Rao, V. J.; Derguini, F.; Nakanishi, K.; Taguchi, T.; Hosoda, A.; Hanzawa, Y.; Kobayashi, Y.; Pande, C.; Callender, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 6077. (b) Mead, D.; Asato, A. E.; Denny, M.; Liu, R. S. H.; Hanzawa, Y.; Taguchi, T.; Yamada, A.; Kobayashi, N.; Hosoda, A.; Kobayashi, Y. *Tetrahedron Lett.* **1987**, *28*, 259. Synthesis of the trifluoro analogue of retinal: (c) Mead, D.; Loh, R.; Asato, A. E.; Liu, R. S. H. *Ibid.* **1985**, *26*, 2873. (d) Hanzawa, Y.; Kawagoe, K.; Kobayashi, N.; Ohshima, T.; Kobayashi, Y. *Ibid.* **1985**, *26*, 2877. (e) Hanzawa, Y.; Yamada, A.; Kobayashi, Y. *Ibid.* **1985**, *26*, 2881. (f) Taguchi, T.; Hosoda, A.; Kobayashi, Y. *Ibid.* **1985**, *26*, 6209.

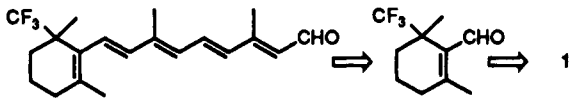
(27) Childs, R. F.; Shaw, G. S.; Lock, C. J. L. *J. Am. Chem. Soc.* **1989**, *111*, 5424 and references cited therein.

Table IV. Reduction of 23 with Various Hydride Reagents at 0 °C

hydride	yield[a] (%) of 24	ratio[b] of 24a/24b	solvent
$NaBH_4$	83	1.7/1	EtOH
DIBAL-H	90	1/2	CH_2Cl_2
$Li(s\text{-}Bu)_3BH$	60	1.4/1	THF
$Li(O\text{-}t\text{Bu})_3AlH$	95	2.6/1	Et_2O
$K(O\text{-}i\text{-}Pr)_3BH$	93	1.8/1	THF

[a] Isolated yield. [b] Determined by NMR (^1H and ^{19}F).

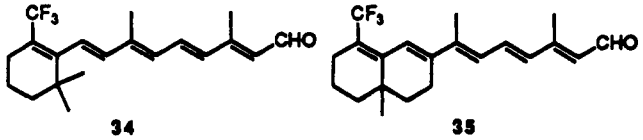
purpose of obtaining further information on the hydrophobic binding site of the retinal-binding protein, 16,16,16-trifluororetinal (4) has been chosen as the target molecule. Since the introduction of fluorine atoms into C16 of the retinal molecule[7] causes the quaternary carbon C1 to become asymmetric, the trifluoromethyl group in each enantiomer might induce different effects. Retrosynthetically, fluorinated β-cyclocitral 29, a key intermediate for the synthesis of 16,16,16-trifluororetinal (4), can be taken back to an ester derivative of 1 whose Diels–Alder reactivity has been established as described.



4 29

For the synthesis of 4, reaction sequences are shown in Scheme III. The Diels–Alder adduct of 2 with 16 is advantageous for an optical resolution of intermediates.[28] In the [2,3]-Wittig rearrangement[29,30] of the tri-*n*-butylstannylmethyl ether of 24, each diastereomer gave different yields of the rearranged product 25. The stannylmethyl ether from the more polar alcohol 24a gave a higher yield (45%) of the rearranged product than that (19%) from the stannylmethyl ether of the less polar alcohol 24b. From the diastereomeric ratios of the reduction of 23 with several metal hydride reagents (Table IV), 23 was reduced by lithium tri-*tert*-butoxyaluminum hydride to give the desired isomer 24a in a ratio of 2.6:1 (95%). Although no determination was made of the relative stereochemistry of the diastereomeric alcohols 24a and 24b and rearranged product 25, the individual susceptibility of 24a and 24b in the Wittig anionic rearrangement could be the result of the electronic repulsive interaction between the trifluoromethyl group and the migrating anion in the cyclic transition state. The acid-catalyzed Claisen rearrangement of the diastereomeric alcohol 24 [$(EtO)_3CCH_3/H_3O^+$/120 °C] gave ester 26 in 70% yield without any significant difference between the diastereoisomers 24a and 24b. Although the Claisen rearrangement product 26, a diastereomeric mixture, was converted to acetylenic alcohol 28 via aldehyde 27, the double bond in the cyclohexene ring was not susceptible to mild isomerization, an important step for the retinal molecule. In the Wittig rearranged product 25, isomerization[31] of the double bond was effected by oxidation of the alcohol group of 25 (CrO_3·2Py, Celite, CH_2Cl_2) to the aldehyde and subsequent treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, Et_2O, 0 °C) to give fluoro analogue 29 of the β-cyclocitral (60 % from 25). The converson of 29 to retinal analogue 4 was carried out effectively by an established procedure[26] as shown in Scheme III.

Comparison of the absorption spectrum of 4 with other trifluororetinals 34[26a] and 35[32] indicated interesting features. The absorption maxima of 18,18,18-trifluororetinal (34)[26a] and 4 in MeOH both appeared at 362 nm. In contrast, 6s-trans fixed 5-CF_3-retinal (35)[32] exhibited an absorption maximum of 382 nm. This hypsochromic shift in 34 and 4 is the result of the torsion between the ring and polyenal side chain, since the retinal analogue 35 possesses a greater degree of π-electron overlap of the ring with the conjugated side chain by locking of the 6s bond of retinal to s-trans (molecular flattening). In 34, the electron-withdrawing trifluoromethyl group destabilizes the excited state of the conjugated system, causing a hypsochromic shift of the absorption maximum,[26a] while, in 4, the trifluoromethyl group exerts no such electronic effect on the conjugated system since the trifluoromethyl group is located on a nonconjugated carbon.[33] The ring-chain torsional angle in 4 may thus possibly be larger than that of 34, whose electronegative trifluoromethyl group is located on the conjugated system.



34 35

Conclusions

For construction of the trifluoromethylated quaternary carbons, 2-(trifluoromethyl)propenoic acid (1) and esters 2 and 3 were used effectively as dienophiles in the Diels–Alder reaction. The $TiCl_4$-catalyzed diastereoselective Diels–Alder reaction of 2-(trifluoromethyl)propenoate ester 3 of D-pantolactone showed excellent asymmetric induction at the trifluoromethylated quaternary carbon, and the absolute configuration was determined to be *R* by X-ray analysis of the adduct 20. The Diels–Alder reaction of 2 with methylated Danishefsky diene 16 followed by introduction of the side chain through the [2,3]-Wittig rearrangement gave trifluoro-β-cyclocitral (29). Thereafter, standard chain extension of 29 afforded 16,16,16-trifluororetinal (4) as an important analogue of the chromophore of the retinal-binding protein.

Experimental Section

Melting points are uncorrected. Capillary gas chromatography was performed with a 25 m × 2.25 mm column (OV-101). Medium pressure column chromatography (MPLC) was performed with a silica gel prepacked column with a UV detector. ^1H NMR spectra were recorded at 400 MHz. ^{19}F NMR spectra were recorded on a 56.4-MHz or 376.3-MHz instrument. Fluorine chemical shifts were reported in parts per million from external benzotrifluoride (BTF) signal and the higher field resonance from the BTF signal was assigned as negative. The purity of all title compounds without combustion analyses was judged to be ≥90% on the basis of ^1H and ^{19}F NMR spectra. In the workup of reaction mixtures, extraction was carried out three times with the indicated

(28) Ester 18 was converted to diastereomeric ester by treating with optically pure phenethyl alcohol in the presence of $Ti(O\text{-}i\text{-}Pr)_4$ as a catalyst. A mixture of diastereomeric esters was separated by MPLC. For the ester exchange reaction with $Ti(O\text{-}i\text{-}Pr)_4$ catalysis, see: (a) Schnurrenberger, P.; Zuger, M. F.; Seebach, D. *Helv. Chem. Acta* **1982**, *65*, 1197. (b) Takeuchi, Y.; Asahina, M.; Murayama, A.; Hori, K.; Koizumi, T. *J. Org. Chem.* **1986**, *51*, 955.

(29) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

(30) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927.

(31) Isomerization of the α-cyclocitral to the β-isomer under basic conditions: Rosenberger, M.; Saucy, G. Ger. Offen 2,520,185; *Chem. Abstr.* **1976**, *84*, 121303u.

(32) Suzuki, M. Unpublished results.

(33) Destabilizing effect of the trifluoromethyl group was estimated by comparing 35 with 6s-trans fixed retinal of the hydrocarbon system reported by Lugtenburg et al., since in both analogues, there is the similar π-overlapping in the conjugated system (similar molecular flattening). Steen, R.; Biesheuvel, P. L.; Mathies, R. A.; Lugtenburg, J. *J. Am. Chem. Soc.* **1986**, *108*, 6410.

solvent and the combined organic phases were washed with 1 N HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl before being dried ($MgSO_4$) unless otherwise described. The filtrate was concentrated under vacuum.

4-*exo*- and 4-*endo*-(Trifluoromethyl)bicyclo[2.2.1]hept-6-ene-4-carboxylic Acids (endo-COOH (5a) and exo-COOH (5b)). To a solution of 1 (0.5 g, 3.5 mmol) in CH_2Cl_2 (5 mL) was added cyclopentadiene (0.28 g, 4.2 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. Evaporation of the solvent gave adduct 5 (0.59 g, 81%, **5a**/**5b** = 2/1). The mixture (200 mg) was dissolved in saturated $NaHCO_3$ (5 mL) and treated with excess I_2–KI solution (I_2 245 mg, KI 1.4 g in H_2O 10 mL). After the mixture was stirred at room temperature for 2 h, the solution was extracted with ether. The combined ether layers were washed with 5% aqueous $Na_2S_2O_3$, H_2O, and saturated aqueous NaCl before being dried ($MgSO_4$). Removal of the solvent gave iodo lactone 7 (212 mg, 66%): mp 65–66 °C; IR (CCl_4) ν 1800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05–2.12 (2 H, m), 2.20 (1 H, dd, J = 4, 14 Hz), 2.45 (1 H, d, J = 11.8 Hz), 2.8 (1 H, bs), 3.39 (1 H, d, J = 5.2 Hz), 3.88 (1 H, d, J = 2.7 Hz), 5.16 (1 H, d, J = 5.2 Hz); ^{19}F NMR ($CDCl_3$) ppm −8.0 (s); MS m/z 332 (M^+). Anal. Calcd for $C_9H_8O_2F_3I$: C, 32.55; H, 2.43. Found: C, 32.84; H, 2.43.

The above aqueous layer was made acidic with 1 N HCl and extracted with ether. The combined organic layer was dried ($MgSO_4$). Concentration of the filtrate gave **5b** (exo-COOH) (60 mg): mp 87–88 °C; ^1H NMR ($CDCl_3$) δ 1.42 (1 H, d, J = 8.8 Hz), 1.48–1.54 (2 H, m), 2.6 (1 H, dd, J = 13.6, 3.5 Hz), 3.01 (1 H, br), 3.49–3.51 (1 H, br), 6.07 (1 H, m), 6.33 (1 H, dd, J = 5.5, 3.0 Hz); ^{19}F NMR ($CDCl_3$) ppm −1.53 (s). Anal. Calcd for $C_9H_9O_2F_3$: C, 52.43; H, 4.40. Found: C, 52.37; H, 4.39.

A solution of the iodo lactone 7 (1.5 g, 4.5 mmol) in ethanol (10 mL) was heated to reflux in the presence of Zn powder (792 mg), and the mixture was stirred at the same temperature for 1 h. The cooled mixture was filtered and concentrted to give a crude material, which was dissolved in saturated aqueous $NaHCO_3$ and washed with ether. The aqueous layer was acidified with 1 N HCl and extracted with ether. The aqueous layer was acidified with 1 N HCl and extracted with ether. Removal of the solvent gave pure crystals of **5a** (endo-COOH): mp 75 °C (713 mg, 77%); IR (KBr) ν3100, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (1 H, d, J = 9.2 Hz), 1.8 (1 H, d, J = 9.2 Hz), 2.04 and 2.06 (2 H, AB q, J = 12.9 Hz), 3.0 (1 H, bs), 3.39 (1 H, bs), 6.11 (1 H, dd, J = 5.7, 3.0 Hz), 6.34 (1 H, dd, J = 5.7, 3.0 Hz); ^{19}F NMR ($CDCl_3$) ppm −2.6 (s); HRMS calcd for $C_9H_9O_2F_3$ 206.0543, found 206.0539. Anal. Calcd for $C_9H_9O_2F_3$: C, 52.43; H, 4.40. Found: C, 52.34; H, 4.39.

1-Methyl-4-(trifluoromethyl)-2-oxabicyclo[2.2.2]octan-3-one (13). A solution of 1 (500 mg, 3.5 mmol) and isoprene (0.35 mL, 4.2 mmol) in CH_2Cl_2 (10 mL) was sealed in a tube and heated at 120 °C for 2 days. Concentration of the reaction mixture by a vacuum line and sublimation (100 °C/15 mmHg) of the crude crystals gave colorless crystals of 8 (545 mg, 74%, a mixture of regioisomers, 10:1 ratio). A mixture of the regioisomers (150 mg) was dissolved into saturated aqueous $NaHCO_3$ and treated with aqueous I_2–KI solution (I_2 182 mg, KI 1.07 g in H_2O 8 mL). After being stirred at room temperature for 1.5 h, the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with 5% aqueous $Na_2S_2O_3$, H_2O, and saturated aqueous NaCl before being dried ($MgSO_4$). Concentration of the filtered solution gave an oily residue. Purification by MPLC (hexane/EtOAc = 10/1) gave iodo lactones 11 and 12 in 58% yield. Less polar isomer 12 (20 mg): IR (CCl_4) ν 1800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (1 H, m), 2.09 (3 H, s), 2.05 (2 H, m), 2.45 (1 H, d, J = 18 Hz), 2.74 (1 H, m), 3.08 (1 H, d, J = 12.3 Hz), 4.7 (1 H, d, J = 6.2 Hz); ^{19}F NMR ($CDCl_3$) ppm −10.0 (s). More polar isomer 11 (110 mg): IR (CCl_4) ν 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6 (3 H, s), 1.95–2.25 (3 H, m), 2.5 (1 H, dd, J = 5.7, 14.6 Hz), 2.6 (1 H, M), 2.95 (1 H, m), 4.1 (1 H, m); ^{19}F NMR ($CDCl_3$) ppm −10.5 (s).

A solution of the more polar iodo lactone 11 (110 mg), Bu_3SnH (0.54 mmol), and catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) in benzene (5 mL) was heated at 50 °C for 2 h. After removal of the solvent, the residue was diluted with ether (5 mL) and then stirred with 10% aqueous KF for 30 min. The suspension was filtered through Celite, and the filtrate was diluted with ether. The organic phase was washed with saturated aqueous NaCl and dried ($MgSO_4$) before concentration. The crude residue was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to give colorless crystals of 13 (57 mg, 83%): mp 95 °C; IR (CCl_4) ν 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (3 H, s), 2.0 (8 H, br); ^{19}F NMR ($CDCl_3$) ppm −10.5 (s); ^{13}C NMR ($CDCl_3$) ppm 23.5, 25, 30, 46 (q, J_{C-F} = 27.4 Hz), 82, 125 (q, J_{C-F} = 279 Hz), 169; MS (Cl) m/z 209 (M + 1).

3a,6,7,7a-Tetrahydro-7a-(trifluoromethyl)-1(3*H*)-isobenzofuranone (14). A solution of 1 (750 mg, 5.35 mmol) and 2,4-pentadien-1-ol[16] in benzene (5 mL) was sealed in a tube and heated at 110 °C for 14 h. The cooled mixture was concentrated in vacuo to give a crude oil. Purification of the crude product by column chromatography on silica gel (hexane/EtOAc = 10/1) gave volatile oil 14 (595 mg, 48%): IR (CCl_4) ν 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8–2.3 (4 H, m), 3.28 (1 H, bs), 4.0 (1 H, d, J = 8 Hz), 4.55 (1 H, d, J = 8 Hz), 5.67 (1 H, d, J = 10 Hz), 5.99 (1 H, m); ^{19}F NMR ($CDCl_3$) ppm −8.2 (s); HRMS calcd for $C_9H_9F_3O_2$ 206.0553, found 206.0521.

2,4-Pentadienyl 2-(Trifluoromethyl)propenoate (15). To a solution of 2,4-pentadien-1-ol[16] (250 mg, 2.97 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (375 mg, 3.7 mmol) in a dropwise manner at −78 °C. After the mixture was stirred at the same temperature for 15 min, 2-(trifluoromethyl)propenoyl chloride[17] (540 mg, 3.41 mmol) was added, and the mixture was stirred for 50 min at −78 °C. The mixture was poured into ice–H_2O and extracted with ether. The extract was concentrated in vacuo to give a crude oil. Purification of the crude product by column chromatography on silica gel (hexane/EtOAc = 7/1) gave pure 15 as a colorless oil (457 mg, 75%): IR (neat) ν 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.78 (2 H, d, J = 6.1 Hz), 5.17 (1 H, d, J = 8.0 Hz), 5.28 (1 H, m), 5.8 (1 H, dt, J = 6.1, 14.1 Hz), 6.29–6.7 (2 H, m), 6.44 (1 H, bs), 6.73 (1 H, bs); ^{19}F NMR ($CDCl_3$) ppm −1.6 (s).

2,2,2-Trifluoroethyl 1-(Trifluoromethyl)-4-oxo-2-cyclohexene-1-carboxylate (17). To a solution of Danishefsky's diene[19] (1.5 g, 9 mmol) in CH_2Cl_2 (5 mL) was added a solution of 2 (2 g, 9 mmol) in CH_2Cl_2 (5 mL) at 0 °C under an argon atmosphere, and the mixture was stirred at room temperature for 5 min. After concentration of the reaction mixture, the residue was treated with p-TsOH (140 mg, 0.74 mmol) in methanol (20 mL). The resulting mixture was stirred at room temperature for 1 h. After evaporating the solvent in vacuo, the residue was distilled at 140 °C/3 mmHg (bulb-to-bulb distillation) to give 17 (1.5 g, 78%): IR (CCl_4) ν 1760, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1–2.7 (4 H, m), 4.6 (2 H, m), 6.27 (1 H, d, J = 10 Hz), 6.90 (1 H, d, J = 10 Hz); ^{19}F NMF ($CDCl_3$) ppm −7.8 (s), −9.6 (t, J_{H-F} = 8.5 Hz), 1:1 ratio; MS (CI) m/z 291 (M + 1).

2,2,2-Trifluoroethyl 4-Methyl-1-(trifluoromethyl)-3-cyclohexene-1-carboxylate (9). $EtAlCl_2$-Catalyzed Reaction. $EtAlCl_2$ (1 M solution in hexane, 0.8 equiv) was added to a mixture of 2 (500 mg, 2.5 mmol) and isoprene (170 mg, 2.5 mmol) in CH_2Cl_2 at −23 °C. Aftering the mixture was stirred for 1 h at the same temperature, saturated aqueous $NaHCO_3$ was added to the reaction mixture at 0 °C. The mixture was extracted with ether. The crude oil was purified by bulb-to-bulb distillation at 100 °C/10 mmHg to give 9 (336 mg, 51%): IR (neat) ν 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (3 H, s), 1.85 (1 H, m), 2.0–2.15 (2 H, br), 2.31–2.41 (2 H, m), 2.77 (1 H, bd, J = 15 Hz), 4.47–4.61 (2 H, m), 5.35 (1 H, bs); ^{19}F NMR ($CDCl_3$) ppm −11.20 (t, J_{H-F} = 8.28 Hz), −11.30 (s), 1:1 ratio; HRMS calcd for $C_{11}H_{12}F_6O_2$ 290.0741, found 290.0753.

$TiCl_2$(O-*i*-Pr)$_2$-Catalyzed Reaction. A solution of $TiCl_2$(O-*i*-Pr)$_2$ prepared from Ti(O-*i*-Pr)$_4$ (0.5 equiv) and $TiCl_4$ (0.5 equiv) in CH_2Cl_2 (0.5 mL) was added to a solution of 2 and isoprene (30 equiv) in CH_2Cl_2 (0.5 mL) at 0 °C, and the mixture was stirred overnight at room temperature. The reaction mixture was worked up as in the case of $EtAlCl_2$.

(3*R*)-Tetrahydro-4,4-dimethyl-2-oxofur-3-yl 2-(Trifluoromethyl)propenoate (3). Under an argon atmosphere, 2-(trifluoromethyl)propenoyl chloride[17] (1.45 g, 10 mmol) was added to a cold (−40 °C) solution of D-pantolactone (1 g, 7.7 mmol) and Et_3N (1.2 mL) in anhydrous CH_2Cl_2 (10 mL). The solution was stirred for 1 h at the same temperature. The reaction mixture was poured into ice–water and the solution was extracted with ether. The crude oil was purified by short column chromatography on silica gel (hexane/EtOAc = 5/1) to afford pure 3 (1.6 g, 85%): mp 41 °C; IR (neat) ν 1790, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (3 H, s), 1.23 (3 H, s), 4.06 and 4.10 (2 H, AB q, J = 9.05 Hz), 5.47 (1 H, s), 6.59 (1 H, q, J_{H-F} = 1.18 Hz) 6.85 (1 H, q, J_{H-F} =

1.7 Hz); ^{19}F NMR ($CDCl_3$) ppm −1.6; $[\alpha]_D$ +10.79° (c 1.13, $CHCl_3$); MS (CI) 253 (M + 1). Anal. Calcd for $C_{10}H_{11}O_4F_3$: C, 47.63; H, 4.37. Found: C, 47.75; H, 4.38.

General Procedure for the Diels–Alder Reaction of 3 Catalyzed by Lewis Acids. Under an argon atmosphere, Lewis acid (0.13 equiv) was added to a cold (−23 °C) solution of **3** (1 equiv) in anhydrous CH_2Cl_2/hexane (ratio 7/1). While the mixture was being stirred for 30 min at −23 °C, the mixture became yellow. The diene (1.6 equiv) was added to the mixture at −23 °C, and the mixture was stirred for 1 h at −23 °C or room temperature. The reaction was quenched by the addition of $Na_2CO_3 \cdot 10H_2O$ powder. On warming to room temperature and stirring, precipitates were formed. The reaction mixture was filtered through Celite and concentrated in vacuo. The product was purified by column chromatography on silica gel to afford the products.

Adduct 20 from butadiene and 3: colorless cyrstals, mp 84 °C; IR ($CHCl_3$) ν 1790, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (3 H, s), 1.18 (3 H, s), 1.87 (1 H, m), 2.18 (1 H, bd, J = 17 Hz), 2.32–2.45 (3 H, m), 2.80 (1 H, bd, J = 17 Hz), 4.04 and 4.06 (2 H, AB q, J = 9.2 Hz), 5.45 (1 H, s), 5.66–5.76 (2 H, m); ^{19}F NMR ($CDCl_3$) ppm −11.06 (s); $[\alpha]_D$ +26.4° (c 0.856, $CHCl_3$); HRMS calcd for $C_{14}H_{17}O_4F_3$ 306.1078, found 306.1098. Anal. Calcd for $C_{14}H_{17}O_4F_3$: C, 54.90; H, 5.59. Found: C, 54.86; H, 5.59.

Adduct 10 from isoprene and 3: colorless crystals, mp 64 °C; IR ($CHCl_3$) ν 1790, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (3 H, s), 1.17 (3 H, s), 1.67 (3 H, s), 1.90 (1 H, m), 2.05 (1 H, bd, J = 18 Hz), 2.28–2.43 (3 H, br), 2.78 (1 H, bd, J = 18 Hz), 4.04 and 4.06 (2 H, AB q, J = 9.1 Hz), 5.39 (1 H, bd, J = 4.2 Hz), 5.43 (1 H, s); ^{19}F NMR ($CDCl_3$) ppm −10.8 (s); $[\alpha]_D$ +36.66° (c 0.96, $CHCl_3$); HRMS calcd for $C_{15}H_{19}O_4F_3$ 320.1233, found 320.1204. Anal. Calcd for $C_{15}H_{19}O_4F_3$: C, 56.29; H, 5.98. Found: C, 56.32; H, 6.02.

Adduct 6 from Cyclopentadiene and 3. 6a (endo-COOR): IR (neat) ν 1790, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (3 H, s), 1.19 (3 H, s), 1.50 (1 H, d, J = 9 Hz), 1.79 (1 H, d, J = 9.1 Hz), 2.12 (2 H, bs) 3.00 (1 H, bs), 3.42 (1 H, bs), 4.00 and 4.04 (2 H, AB q, J = 9.02 Hz), 5.27 (1 H, s), 6.08 (1 H, dd, J = 5.6, 3.0 Hz), 6.37 (1 H, dd, J = 5.6, 3.0 Hz); ^{19}F NMR ($CDCl_3$) ppm −4.04 (s). **6b** (exo-COOR): ^1H NMR ($CDCl_3$) δ 1.16 (3 H, s), 1.22 (3 H, s), 1.44 (1 H, d, J = 8.6 Hz), 1.52 (1 H, d, J = 8.6 Hz), 1.57 (1 H, d, J = 12.4 Hz), 2.65 (1 H, dd, J = 12.4, 3.6 Hz), 3.0 (1 H, bs), 3.52 (1 H, bs), 4.05 and 4.07 (2 H, AB q, J = 9.02 Hz), 6.08 (1 H, m), 6.37 (1 H, dd, J = 5.6, 3.1 Hz); ^{19}F NMR ($CDCl_3$) ppm −1.81 (s). The endo/exo ratio was 8:1.

Product 19 from 1-Methoxy-2-methyl-3-(trimethylsiloxy)-1,3-butadiene (16)[24] and 3. Major diastereomer of **19**: IR (neat) ν 1790, 1750, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (3 H, s), 1.88 (3 H, s), 2.4–2.7 (4 H, br), 4.05 (2 H, m), 5.4 (1 H, s), 6.67 (1 H, s); ^{19}F NMR ($CDCl_3$) ppm −8.3 (s); MS (EI) m/z 334 (M^+). Minor diastereomer of **19**: ^1H NMR ($CDCl_3$) δ 1.1 (3 H, s), 1.21 (3 H, s), 1.87 (3 H, s), 2.37–2.65 (4 H, br), 4.05 (2 H, m), 5.39 (1 H, s), 6.63 (1 H, s); ^{19}F NMR ($CDCl_3$) ppm −7.8 (s). The diastereomeric ratio was 3.3:1.

General Procedure for Hydrolysis by LiOH. A mixture of the Diels–Alder adduct, $LiOH \cdot H_2O$ (4 equiv) in THF/H_2O (5/4) (10 mL) was stirred overnight. After removal of most of THF in vacuo, the residual aqueous solution was acidified with 1 N HCl. The mixture was extracted with ether, and the combined organic layers were dried over $MgSO_4$. The filtrate was concentrated in vacuo to give crystals, which were purified by sublimation.

(*R*)-1-(Trifluoromethyl)-3-cyclohexene-1-carboxylic acid (21): colorless crystals, mp 86 °C; IR ($CHCl_3$) ν 3100, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (1 H, m), 2.15–2.4 (5 H, br), 2.7 (1 H, bd, J = 15.5 Hz), 5.7 (2 H, m); ^{19}F NMR ($CDCl_3$) ppm −11.45 (s); $[\alpha]_D$ + 72.35° (c 0.246, $CHCl_3$); HRMS calcd for $C_8H_9O_2F_3$ 194.0552, found 194.0553.

(*R*)-1-(Trifluoromethyl)-4-methyl-3-cyclohexene-1-carboxylic acid ((*R*)-8a): colorless crystals, mp 108 °C; IR ($CHCl_3$) ν 3100, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (3 H, s), 1.85 (1 H, m), 1.99–2.73 (5 H, m), 2.71 (1 H, bd, J = 1.7 Hz), 5.36 (1 H, bs); ^{19}F NMR ($CDCl_3$) ppm −11.23 (s); $[\alpha]_D$ +65.7° (c 0.7, $CHCl_3$); HRMS calcd for $C_9H_{11}O_2F_3$ 208.0710, found 208.0723. Anal. Calcd for $C_9H_{11}O_2F_3$: C, 51.93: H, 5.3. Found: C, 51.86; H, 5.3.

2,2,2-Trifluoroethyl 1-(Trifluoromethyl)-3-methyl-4-oxo-2-cyclohexene-1-carboxylate (18). To a solution of **16** (10 g, 54 mmol) in CH_2Cl_2 (25 mL) was added a solution of **2** (11.8 g, 54 mmol) in CH_2Cl_2 (15 mL) at 0 °C under an argon atmosphere, and the solution was stirred for 3 min. After evaporating the solvent, methanol (30 mL) and *p*-TsOH (2 g, 10.5 mmol) were added at 0 °C. The resulting solution was stirred at the same temperature for 1.5 h. Evaporation of the solvent and vacuum distillation of the residue gave **18** (16.5 g, 87%): bp 88 °C/3 mmHg; IR (neat) ν 1765, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.9 (3 H, s), 2.4 (2 H, m), 2.65 (2 H, m), 4.6 (2 H, m), 6.74 (1 H, s); ^{19}F NMR ($CDCl_3$) ppm −8.3 (s), −10.0 (t, J = 8.46 Hz), 1:1 ratio; HRMS calcd for $C_{11}H_{10}F_6O_3$ 304.0533, found 304.0522.

1-(Trifluoromethyl)-3-methyl-4-oxo-2-cyclohexene-1-methanol (22). Under an argon atmosphere, a 1 M solution of diisobutylaluminum hydride (DIBAL-H) in hexane (150 mL, 150 mmol) was added to a solution of **18** (11.4 g, 37.5 mmol) in CH_2Cl_2 (60 mL) at −78 °C, and the mixture was stirred at room temperature for 1.5 h. The reaction was quenched with methanol (30 mL) and 10% H_2SO_4 (50 mL) at 0 °C, and the mixture was extracted with ether. The crude product was chromatographed through a short column on silica gel (hexane/EtOAc = 1/1). MnO_2 (36 g, 0.41 mol) was added to a solution of the obtained diol in CH_2Cl_2 (100 mL), and the solution was stirred for 20 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated to dryness to give crude crystals. Purification by column chromatography on silica gel (hexane/EtOAc = 1/1) gave **22** (4.3 g, 55%): mp 62 °C; IR (CCl_4) ν 3500, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (3 H, s), 2.25 (2 H, t, J = 4.5 Hz), 2.6 (2 H, t, J = 4.5 Hz), 3.85 (2 H, d, J = 3.6 Hz), 6.46 (1 H, s); ^{19}F NMR ($CDCl_3$) ppm −8.9 (s); MS m/z 208 (M^+).

2-Methyl-4-(iodomethyl)-4-(trifluoromethyl)-2-cyclohexen-1-one (23). Under an argon atmosphere, methyltriphenoxyphosphonium iodide[34] (6.4 g, 15.5 mmol) was added to a solution of **22** (1.2 g, 5.7 6mmol) in *N,N*-dimethylformamide (DMF, 8 mL), and the mixture was stirred for 2.5 h. After being quenched by methanol (20 mL) at 0 °C, the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were washed with 10% aqueous $Na_2S_2O_3$, H_2O, and saturated aqueous NaCl before being dried ($MgSO_4$). The filtrate was concentrated to dryness to give a crude oil, which was purified by column chromatography on silica gel (hexane/EtOAc = 5/1) to give **23** (1.56 g, 85%): IR (neat) ν 2960, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (3 H, s) 2.30 (2 H, m), 2.65 (2 H, m), 3.26 and 3.43 (2 H, AB q, J = 12 Hz), 6.25 (1 H, s); ^{19}F NMR ($CDCl_3$) ppm −8.5 (s); MS (CI) m/z 319 (M + 1).

2,4-Dimethyl-4-(trifluoromethyl)-2-cyclohexen-1-ol (24). To a solution of **23** (1.56 g, 5 mmol) in ethanol (10 mL) was added $NaBH_4$ (156 mg, 4.1 mmol) at 0 °C, and the mixture was stirred at the same temperature for 30 min. After addition of 1 N HCl at 0 °C, the reaction mixture was extracted with ether. Removal of the solvent and purification of the residue by flash column chromatography on silica gel (hexane/EtOAc = 10/1) gave a mixture of diastereomers (1.28 g, 83%). Under an argon atmosphere, a benzene solution (30 mL) of a mixture of the diastereomeric alcohols (1.7:1 ratio) (3.43 g, 10.7 mmol), *n*-Bu_3SnH (4.8 g, 16.5 mmol), and AIBN (10 mg) was heated at 50 °C for 1 h. After concentration of the reaction mixture, the residue was diluted with ether (30 mL) and the solution was stirred with 10% aqueous KF (30 mL). The resulting mixture was stirred for 1 h and the precipitates were removed by filtration through Celite. After the organic phase was dried with $MgSO_4$, the filtrate was concentrated to dryness. The residue was purified by column chromatography on silica gel (hexane/CH_2Cl_2/Me_2CO = 10/10/1) to give two separable diastereomers **24a** and **24b** (1.7 g, 83%). More polar isomer **24a**: clear oil; IR (CCl_4) ν 3610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (3 H, s), 1.5 (1 H, d, J = 6.2 Hz), 1.6–1.68 (2 H, m), 1.82 (3 H, bs), 1.86–1.92 (1 H, m), 2.01–2.12 (1 H, m), 4.05 (1 H, bs), 5.35 (1 H, bs); ^{19}F NMR ($CDCl_3$) ppm −13.3 (s); HRMS calcd for $C_9H_{13}F_3O$ 194.0918, found 194.0941. Less polar isomer **24b**: colorless crystals; mp 64 °C; IR (CCl_4) ν 3610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (3 H, s), 1.41–1.51 (2 H, m), 1.8–1.9 (5 H, broad signal including 3-H singlet at 1.84) (6 H, bs), 1.98–2.04 (1 H, m),

(34) Verheyden, J. P. H.; Moffat, J. G. *J. Org. Chem.* **1970**, *35*, 2319.

3.93 (1 H, bs), 5.37 (1 H, s); ^{19}F NMR ($CDCl_3$) ppm -13.7; HRMS calcd for $C_9H_{13}F_3O$ 194.0918, found 194.0886. Anal. Calcd for $C_9H_{13}F_3O$: C, 55.67; H, 6.75. Found: C, 55.60; H, 6.65.

2,6-Dimethyl-6-(trifluoromethyl)-2-cyclohexene-1-methanol (25). Under an argon atmosphere, a solution of **24a** (362 mg, 1.86 mmol) in THF (3 mL) was added to a suspension of KH (90 mg, 2.25 mmol) in THF (2 mL) at 0 °C, and the mixture was stirred for 10 min. To the mixture was added *n*-Bu_3SnCH_2I[29] (805 mg, 1.86 mmol) at 0 °C, and the resulting mixture was stirred for 1 h at room temperature. The mixture was cooled to -78 °C and then a 1.6 M hexane solution of *n*-BuLi (1.4 mL, 2.23 mmol) was added. The mixture was stirred at the same temperature for 1 h. After addition of saturated aqueous NH_4Cl, the mixture was extracted with ether. The crude material was purified by column chromatography on silica gel (hexane/EtoAc = 5/1) to give **25** (175 mg, 45%): IR (neat) ν 3590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.17–1.20 (1 H, m), 1.25 (3 H, s), 1.74–1.82 (4 H, broad signal including 3-H singlet at 1.78), 2.06 (2 H, br), 2.21 (1 H, bs), 3.81–3.90 (2 H, m), 5.73 (1 H, bs); ^{19}F NMR ($CDCl_3$) ppm -11.9 (s); HRMS calcd for $C_{10}H_{15}F_3O$ 208.1075, found 208.1078. In the same manner as for **24a**, alcohol **24b** gave **25** (64 mg, 17%): IR (neat) ν 3600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (3 H, s), 1.31 (1 H, m), 1.55 (1 H, m), 1.77 (3 H, s), 1.95 (1 H, bs), 2.0–2.10 (3 H, m), 3.82 (2 H, bs), 5.63 (1 H, bs); ^{19}F NMR ($CDCl_3$) ppm -10.1 (s).

2,6-Dimethyl-6-(trifluoromethyl)-1-cyclohexenecarboxaldehyde (Trifluoro-β-cyclocitral) (29). To a solution of pyridine (0.37 mL, 4.6 mmol) in CH_2Cl_2 (2 mL) was added CrO_3 (230 mg, 2.3 mmol) at 0 °C, and the mixture was stirred for 15 min at the same temperature. After addition of Celite (230 mg) and stirring of the mixture for 5 min, a solution of **25** (48 mg, 0.23 mmol) in CH_2Cl_2 (1 mL) was added at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. After addition of $NaHSO_3$ (230 mg), the solution was passed through a column of dry silica gel (ether). The eluate was concentrated to $^1/_3$ volume, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) (35 mg, 0.23 mmol) was added, and the resulting mixture was stirred for 2 h. Concentration of the solution in vacuo and purification (silica gel TLC plate, pentane/ether = 5/1) gave **29** (28 mg, 59%) as a clear oil: IR (CCl_4) ν 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.51 (3 H, s), 1.53–1.70 (3 H, m), 1.85 (1 H, m), 2.13 (3 H, s), 2.20 (2 H, m), 10.06 (1 H, s); ^{19}F NMR ($CDCl_3$) ppm -7.3 (s); HRMS calcd for $C_{10}H_{13}F_3O$ 206.0918; found 206.0940.

Methyl (2*E*,4*E*)-3-Methyl-5-(2,6-dimethyl-6-(trifluoromethyl)-1-cyclohexen-1-yl)-2,4-pentadienoate (30). Under an argon atmosphere, *n*-BuLi in hexane (1.5 M solution, 0.58 mL, 0.84 mmol) was added to a solution of methyl 4-(diethylphosphono)-3-methyl-2-butenoate (**33**)[35] (246 mg, 0.98 mmol) at -78 °C, and the mixture was stirred at room temperature for 30 min and then cooled to -78 °C. To the cold solution was added a solution of aldehyde **29** (58 mg, 0.28 mmol) in THF (2 mL), and the mixture was stirred at room temperature for 1 h. After the addition of saturated aqueous NH_4Cl, the reaction mixture was extracted with ether. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 25/1) to give **30** as a clear oil (38 mg, 38%): IR (neat) ν 1720 cm^{-1}; ^{1}H NMR[7] ($CDCl_3$) δ 1.23 (3 H, s, 1-Me), 1.6 (2 H, bs), 1.71 (3 H, s, 5-Me), 1.93–2.11 (4 H, m), 2.32 (3 H, s, 9-Me), 3.71 (3 H, s, CO_2Me), 5.74 (1 H, s, 10-H), 6.04 (1 H, d, J = 15.8 Hz, 8-H), 6.46 (1 H, d, J = 15.8 Hz, 7-H); ^{19}F NMR ($CDCl_3$) ppm -9.5 (s); HRMS calcd for $C_{16}H_{21}F_3O_2$ 302.1492, found 302.1471.

(2*E*,4*E*)-3-Methyl-5-(2,6-dimethyl-6-(trifluoromethyl)-1-cyclohexen-1-yl)-2,4-pentadienal (31). Under an argon atmosphere, DIBAL-H (1.0 M in hexane, 0.28 mL) was added to a solution of **30** (31 mg, 0.10 mmol) in hexane–ether (1:1, 1 mL) at -78 °C, and the mixture was stirred at the same temperature for 10 min. After the addition of silica gel (300 mg), H_2O (50 μL), and hexane–ether (1:1, about 0.2 mL) to a reaction mixture at -78 °C, the resulting mixture was stirred at 0 °C for 1 h. The mixture was filtered through Celite/$MgSO_4$ (1:1) and the filtrate was diluted with CH_2Cl_2 (5 mL) and then stirred with MnO_2 (170 mg, 1.9 mmol) for 5 min. The mixture was filtered through Celite/$MgSO_4$ and the filtrate was concentrated to dryness. The residue was purified by MPLC (hexane/EtOAc = 20/1) to give **31** (17 mg, 61%): ^{1}H NMR[7] ($CDCl_3$) δ 1.25 (3 H, s, 1-CH_3), 1.5–1.9 (4 H, m), 1.8 (3 H, s, 5-Me), 2.1 (2 H, m), 2.3 (3 H, s, 9-Me), 6.0 (1 H, d, J = 7.5 Hz, 10-H), 6.2 (1 H, d, J = 13.5 Hz, 8-H), 6.7 (1 H, d, J = 13.5 Hz, 7-H), 10.15 (1 H, d, J = 7.5 Hz, CHO); ^{19}F NMR ($CDCl_3$) ppm -7.56.

Methyl 16,16,16-Trifluororetinoate (32).[7] The aldehyde **31** (17 mg, 0.063 mmol) was treated with **33** as in the case of **29** to give a mixture of all-trans and 13-cis esters **32** in 47% yield, which were separated by MPLC (hexane/EtOAc = 50/1) to give *all-trans*-**32** (11 mg) and 13-*cis*-**32** (3 mg). ***all-trans*-32**: ^{1}H NMR ($CDCl_3$) δ 1.22 (3 H, s, 1-Me), 1.5–1.7 (4 H, bs), 1.76 (3 H, s, 5-Me), 1.99 (3 H, s, 9-Me), 2.0–2.15 (2 H, m), 2.35 (3 H, s, 13-Me), 3.71 (3 H, s, COOMe), 5.78 (1 H, s, 14-H), 6.08 (1 H, d, J = 15.9 Hz, 8-H), 6.14 (1 H, d, J = 11 Hz, 10-H), 6.17 (1 H, d, J = 15.9 Hz, 7-H), 6.30 (1 H, d, J = 15 Hz, 12-H), 6.99 (1 H, dd, J = 11, 15 Hz, 11-H). **13-*cis*-32**: ^{1}H NMR[7] ($CDCl_3$) δ 1.22 (3 H, s, 1-Me), 1.5–1.7 (4 H, bs), 1.76 (3 H, s, 5-Me), 1.98 (3 H, s, 9-Me), 2.07 (3 H, s, 13-Me), 2.05–2.15 (2 H, m), 3.70 (3 H, s, COOMe), 5.65 (1 H, s, 14-H), 6.09 (1 H, d, J = 16 Hz, 8-H), 6.15 (1 H, d, J = 16 Hz, 7-H), 6.21 (1 H, d, J = 11.4 Hz, 10-H), 6.96 (1 H, dd, J = 11.4, 15.3 Hz, 11-H), 7.77 (1 H, d, J = 15.3 Hz, 12-H).

16,16,16-Trifluororetinal (4).[7] The all-trans ester **32** (9 mg) was reduced (DIBAL-H) and oxidized (MnO_2) as in the case of **30**. Purification of the crude product by MPLC (hexane/EtOAc = 20/1) in the dark gave retinal **4** (2.4 mg, 33%): ^{1}H NMR[7] ($CDCl_3$) δ 1.23 (3 H, s, 1-Me), 1.5–1.7 (4 H, m), 2.0–2.15 (2 H, m), 1.76 (3 H, s, 5-Me), 2.05 (3 H, s, 9-Me), 2.33 (3 H, s, 13-Me), 5.98 (1 H, d, J = 8 Hz, 14-H), 6.1 (1 H, d, J = 16 Hz, 8-H), 6.18 (1 H, d J = 11.5 Hz, 10-H), 6.24 (1 H, d, J = 16 Hz, 7-H), 6.37 (1 H, d, J = 15 Hz, 12-H), 7.12 (1 H, dd, J = 11.5, 15 Hz, 11-H), 10.11 (1 H, d, J = 8 Hz, CHO); ^{19}F NMR ($CDCl_3$) ppm -9.02; HRMS calcd for $C_{20}H_{25}F_3O$ 338.1856, found 338.1887.

Supplementary Material Available: X-ray data and NMR spectra for compounds without combustion analyses (31 pages). Ordering information is given on any current masthead page.

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