Stereoselectivity and Generality of the Palladium-Catalysed Cyclopropanation of α,β-Unsaturated Carboxylic Acids Derivatized with Oppolzer's Sultam

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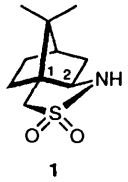
A series of α,β-unsaturated carboxylic acids derivatized with camphorsultam **1** as a chiral auxiliary has been stereoselectively cyclopropanated. The selectivity of the reaction produces cyclopropanated products with the 1*R*,2*R* absolute configuration as indicated by the optical rotations as well as by an X-ray structure determination. The temperature dependence of the reaction was studied with three substrates. The highest stereoselectivity was obtained at temperatures above 25 °C. Branching at the α- or β-carbons disfavours complete conversion, and electron-withdrawing substituents at these positions seem to prevent the reaction. The auxiliary was removed by using titanium(IV) isopropoxide in benzyl alcohol followed by alkaline hydrolysis of the intermediate ester. The potent 5-HT_{1A} receptor agonist (1*R*,2*S*)-2-(2-hydroxyphenyl)-*N*,*N*-dipropylcyclopropylamine **13** was synthesized by this method.

Construction of cyclopropyl moieties has attracted considerable interest from organic chemists because of the unique properties of the cyclopropane ring[1] and its occurrence in numerous natural products.[2] In addition, the cyclopropyl moiety is present in various drugs of potential therapeutic use, including enzyme inhibitors (in particular of monoamine oxidase)[3] and selective serotonergic receptor agonists.[4] Consequently, a variety of synthetic routes to cyclopropanes have been developed,[5] some of which are stereoselective in nature.[6,7] Many of these stereoselective cyclopropanations have been performed with chiral catalysts but such reactions frequently produce unsatisfactory enantiopurities and require cumbersome purification procedures. The use of chiral auxiliaries to induce desired stereochemistries produces mixtures of diastereoisomers which are more readily separated. However, only a few methods have been reported in which a chiral auxiliary is used to direct the stereochemistry of a cyclopropanation. These include, *e.g.* (i) a Simmons–Smith reaction of alk-1-enylboronic esters derivatized with dialkyl tartrates, which produces cyclopropanated derivatives with 73–94% de,[8] (ii) a modified Simmons–Smith reaction of allylic alcohols linked to carbohydrates, which proceeds with excellent diastereoselectivity,[9] (iii) a palladium-catalysed addition of diazomethane to β-substituted acrolein derivatives substituted with an ephedrine-derived oxazolidine moiety, which also provides cyclopropane derivatives with high stereoselectivities,[10] and (iv) a Simmons–Smith reaction of enol ethers carrying an optically active 1,3-diol as a chiral auxiliary, providing cleavable cyclopropyl ethers with high stereoselectivity.[11]



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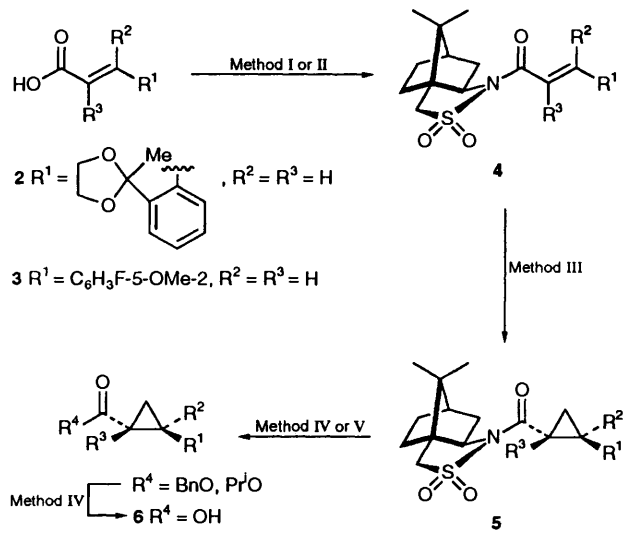
Bornane-10,2-sultam (Oppolzer's sultam; **1**)[12] is another frequently used chiral auxiliary which has been used successfully in a variety of stereoselective reactions including, *e.g.*, OsO_4-catalysed dihydroxylations,[13] Pd-catalysed hydrogenations,[14] other organometallic reactions,[15] hydride reductions,[16] aldol condensations,[17] and several cycloadditions.[18] A major advantage with this particular moiety is related to its propensity to form crystalline derivatives, which facilitates the isolation of reaction products of high diastereoisomeric purity. Recently, we reported that α,β-unsaturated carboxylic acids derivatized with sultam **1** undergo a stereoselective Pd-catalysed cyclopropanation upon treatment with diazomethane.[19] In order to try to assess the scope and limitations of this stereoselective cyclopropanation, we have now extended our investigation and present herein a full account of our studies.

Results and Discussion

Preparation of Substituted Cinnamic Acids.—2'-Bromoacetophenone was coupled with methyl acrylate in a palladium-catalysed reaction to afford the corresponding *E*-cinnamate as a single stereoisomer.[20] The ketone functionality was protected as a ketal and the ester was subjected to alkaline hydrolysis to yield the desired acid **2**. 4-Fluoroanisole was chloromethylated in the 2-position with dimethoxymethane in conc. hydrochloric acid–sulfuric acid and the product was subsequently converted into the aldehyde by a Sommelet reaction.[21] This aldehyde was converted into the corresponding cinnamic acid **3** by a Knoevenagel condensation with malonic acid.[22] The other carboxylic acids used were commercially available.

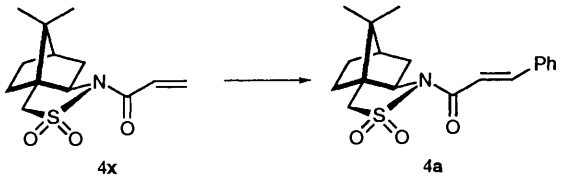
Preparation of Enoyl Sultams.—The carboxylic acids were converted into acid chlorides by treatment with thionyl dichloride or oxalyl dichloride and these were then treated with the preformed sodium salt of sultam **1** to afford enoyl sultams **4a–4x** (Methods I and II, Scheme 1). With the exception of **4a–4v**, pure enoyl sultams were obtained in good yields (67–88%) following recrystallization (Table 1). Compounds **4s–4v** were produced in much lower yields (33–53%), which could not be improved despite considerable experimental effort. An alternative to Methods I and II is to functionalize the preformed parent **4x** by a palladium-catalysed coupling with an



Scheme 1

aryl halide under phase-transfer conditions,[23] *e.g.* coupling between acryloyl sultam **4x** and iodobenzene produces compound **4a** as a single stereoisomer (Method V, Scheme 2).

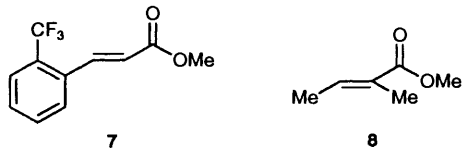
During the preparation of this manuscript, a new method was published in which acid chlorides are coupled with the *N*-trimethylsilyl derivative of camphorsultam in refluxing benzene and in the presence of copper(II) chloride.[24] This might be the method of choice for acids with low stability under the strongly alkaline conditions used in the standard coupling method.



Scheme 2

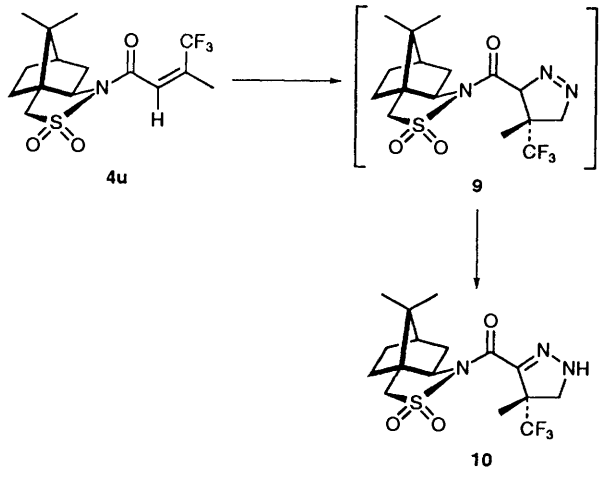
The Cyclopropanation.—Cyclopropanations were performed as follows: the appropriate enoyl sultam was dissolved in CH_2Cl_2 or $ClCH_2CH_2Cl$ and was treated with diazomethane in the presence of 0.005 mol equiv. of palladium(II) acetate, as previously described.[25] According to our experience, larger concentrations of catalyst should be avoided since they often result in precipitation of palladium(0) and subsequent termination of the reaction. The cyclopropanation was performed at 0 °C because preliminary experiments indicated that lower temperatures lead to incomplete reaction, and higher temperatures were avoided because of the volatility of diazomethane.

With the exception of the *para*-cyano-substituted (**4e**) (*vide supra*), the *ortho*-trifluoromethyl-substituted (**4f**) and the *ortho*-(2-methyl-1,3-dioxolan-2-yl)-substituted (**4h**) enoyl sultams containing an aryl moiety in the β-position of the vinyl group were quantitatively converted into cyclopropanated products **5** with 59–92% diastereoisomeric excess (de) under these conditions (yields are given in Table 2). Diastereoisomeric purities above 96% de were obtained following recrystallization. Although we were unable to purify the cyclopropane resulting from compound **4f** to homogeneity, analysis by GC-MS indicated that the crude reaction mixture consisted of 50% of the starting material and 50% of cyclopropanated product (68% de). In a control experiment, methyl ester **7** was quantitatively converted into cyclopropanated product.



The reaction also proceeds well when an alkyl group is present in the β-position of the vinyl moiety (**4n** and **4o**). However, introduction of a second alkyl group in the α- (**4r**) or β-position (**4q**) leads to lower yields (15–30%; GC-MS) while stereoselectivity appears to remain high. We were not able to isolate pure cyclopropane derivatives of compounds **4r** or **4q**. The degree of conversion of methyl ester **8** into cyclopropanated product is much higher than that of compound **4r**, indicating that the rate of the reaction is slowed by the bulky sultam moiety (*vide supra*).

The cyclopropanation of the conjugated diene **4p** produced a non-separable mixture of mono- and di-cyclopropanated isomers in a 3 : 1 ratio according to GC-MS analysis. In contrast, substrates **4s**, **4t**, and **4v** which are substituted with electron-withdrawing groups, did not appear to produce any cyclopropanated products. Similarly, compound **4u** did not produce cyclopropanated products. Instead, we isolated 2-pyrazoline derivative **10** as a single diastereoisomer from the reaction. Presumably, this derivative results from tautomerization of the initially formed pyrazoline **9** (Scheme 3). The stereochemistry of the product was assigned on the basis of the assumption that this reaction proceeds with the same π-face selectivity as the cyclopropanation.



Scheme 3

Preparation of Cyclopropanecarboxylic Acids.—In order to remove the sultam moiety, we treated cyclopropanoyl sultams **5a–5c**, and **5m** with titanium(IV) isopropoxide in benzyl alcohol.[26] Attempts to use ethanol or propan-2-ol failed, probably due to poor solubility of the titanium(IV) isopropoxide in these solvents. The amount of benzyl alcohol was kept at a minimum to simplify the work-up. This procedure resulted in mixtures of benzyl and isopropyl esters which were directly hydrolysed [NaOH, water, MeOH, tetrahydrofuran (THF)] to the corresponding cyclopropanecarboxylic acids (Method IV; Table 3). The conversion of sultam **5n** to the free acid by Method IV resulted in poor yields. Therefore, compound **5n** was hydrolysed directly by treatment with LiOH in THF and was then purified by column chromatography (Method V).

Table 1 Physical, NMR spectroscopic and analytical data of enoyl sultams **4**

Compound	R^1	R^2	R^3	Method[a]	Yield (%)	$[\alpha]_D^{22}$	M.p. (T/°C)	^{13}C Olefin[b] δ_C α/β (ppm)	^1H Olefin[c] δ_H α/β (ppm)	$J_{a,b}$ (Hz)	Found (%) (Required) C	H	N
4a $C_{19}H_{23}NO_3S$	Ph	H	H	I	82	−95.0	189–190	117.4/145.5	7.2/7.8	15.5		*d*	
4b $C_{20}H_{25}NO_4S$	2-$MeOC_6H_4$	H	H	I	84	−90.9	156–158	118.0/141.0	7.3/8.1	15.6	64.15 (64.0	6.85 6.7	3.6 3.7)
4c $C_{20}H_{25}NO_4S$	3-$MeOC_6H_4$	H	H	I	75	−87.3	190–192	117.8/145.5	7.2/7.7	15.5	64.15 (64.0	6.75 6.7	3.6 3.7)
4d $C_{22}H_{29}NO_6S$	3,4,5-$(MeO)_3C_6H_2$	H	H	I	85	−65.7	205–206	116.7/145.5	7.1/7.7	15	60.45 (60.7	6.9 6.7	3.25 3.2)
4e $C_{20}H_{22}N_2O_3S$	4-NCC_6H_4	H	H	II	83	−89.5	251–252	120.9/142.8	7.2/7.7	15.6	64.4 (64.8	5.9 6.0	7.3 7.6)
4f $C_{20}H_{23}F_3NO_3S$	2-$(CF_3)C_6H_4$	H	H	I	83	−77.8	220–221	121.4/140.7	7.2/8.2	15.2	57.5 (58.1	5.1 5.4	3.25 3.4)
(+)-**4g**[e] $C_{20}H_{24}FNO_4S$	2-MeO-5-FC_6H_3	H	H	II	92	+86.4	139–139.5	119.1/139.7	7.3/8.0	15.5	61.0 (61.05	6.2 6.15	3.6 3.6)
(−)-**4g** $C_{20}H_{24}FNO_4S$	2-MeO-5-FC_6H_3	H	H	II	89	−83.2	138.5–140	119.1/139.7	7.3/8.0	15.5	60.6 (61.05	6.1 6.15	3.6 3.6)
(+)-**4h**[e] $C_{23}H_{29}NO_5S$	2-XC_6H_4[f]	H	H	II	98[g]	+70.0	182.5–184	118.5/145.4	7.0/8.6	15.2	64.0 (64.0	7.0 6.8	3.4 3.25)
(−)-**4h** $C_{23}H_{29}NO_5S$	2-XC_6H_4[f]	H	H	II	92[g]	−73.1	182–184	118.5/145.4	7.0/8.6	15.2	64.05 (64.0	7.0 6.8	3.4 3.25)
(+)-**4i**[e] $C_{17}H_{21}NO_3S_2 \cdot 1/4H_2O$	2-Thienyl	H	H	I	86	+93.5	213–215	116.0/137.8	6.9/7.9	15.1	58.25 (58.1	6.15 6.0	4.15 4.0)
(−)-**4i** $C_{17}H_{21}NO_3S_2$	2-Thienyl	H	H	I	71	−92.4	213–215	116.0/137.8	6.9/7.9	15.1	57.45 (57.4	6.1 6.1	3.85 3.9)
4k $C_{17}H_{20}BrNO_3S_2$	4-Br-2-thienyl	H	H	II	68	−76.7	153–155	117.3/136.3	7.0/7.8	15.2	47.45 (47.4	4.75 4.7	3.1 3.25)
4l $C_{17}H_{21}NO_4S \cdot 1/4H_2O$	2-Furyl	H	H	I	78	−92.1	153–158	114.9/131.6	7.0/7.5	14.9	60.0 (60.1	6.35 6.4	4.05 4.1)
4m $C_{23}H_{27}FeNO_3S$	Ferrocenyl	H	H	II	82	+78.8[h]	217–218[i]	114.3/147.1	6.7/7.7	15.0	60.5 (60.9	6.0 6.0	2.85 3.1)
4n $C_{14}H_{21}NO_3S$	Me	H	H	I[j]	77	−99.0	185–187	122.3/146.2	6.6/7.1	14.9		*k*	
4o $C_{23}H_{39}NO_3S$	Decyl	H	H	I[l]	84	−65.9	*m*	120.8/151.1	6.5/7.1	15.1	67.45 (67.4	9.45 9.6	3.35 3.4)
4p $C_{16}H_{23}NO_3S$	Prop-1-enyl	H	H	II	84	−89.9	107–109	118.3/145.8 130.0/141.0	*n*	*n*		*o*	
4q $C_{15}H_{23}NO_3S$	Me	Me	H	II[p]	88	−79.6	125–130[i]	116.0/159.1	6.3		60.9 (60.6	8.1 7.8	4.55 4.7)
4r $C_{15}H_{23}NO_3S$	Me	H	Me	II	80	−76.2	174–176	131.4/137.4	6.4			*q*	
4s $C_{13}H_{18}ClNO_3S$	H	Cl	H	II[l]	33	−96.2	104–106	121.0/133.0	6.7/6.8[r]	8.2	51.35 (51.4	6.1 6.0	4.55 4.6)
4t $C_{13}H_{18}ClNO_3S$	Cl	H	H	II[l]	53	−92.5	170–172	124.2/138.6	7.0/7.4	12.9	51.15 (51.4	6.15 6.0	4.55 4.6)
4u $C_{15}H_{20}F_3NO_3S$	Me	CF_3	H	II[j]	44	−81.5	67–68	162.8/142.0	6.9		51.25 (51.3	5.75 5.7	3.85 4.0)
4v $C_{16}H_{23}NO_5S$	CO_2Et	H	H	I	38	−96.3	118–123	132.2/134.0	6.9/7.5	15.2	56.65 (56.3	6.95 6.8	4.1 4.1)
4x $C_{13}H_{19}NO_3S$	H	H	H	II[j]	67	−97.2	200–202	131.2/127.8 10.3/1.6	6.9/6.5/5.9	16.7		*k*	

[a] D-(−)-Camphorsultam was used unless otherwise noted. [b] Assigned by heteronuclear shift-correlation spectra (HETCOR) when not unambiguous. [c] Assigned by homonuclear shift correlation (COSY) when not unambiguous. [d] Ref. 15a. [e] Prepared from L-(+)-camphorsultam. [f] X = 2-methyl-1,3-dioxolan-2-yl. [g] Not recrystallized due to poor stability. However, an analytical sample was obtained from recrystallization. [h] Determined in a 1.0 cm cell. [i] Decomposition. [j] Prepared from the commercially available acid chloride. [k] Ref. 18a. [l] Purified by flash chromatography. [m] Oil. [n] Not assigned. [o] Ref. 15b. [p] Recrystallized from diethyl ether–hexane. [q] Ref. 13. [r] Not unambiguously assigned.

Table 2 Physical and analytical data of cyclopropanoyl sultams **5**

Compound	de[a] (%)	Yield[b] (%)	de[c] (%)	$[\alpha]_D^{22}$[c,d]	M.p.[c] (T/°C)	MS[e] m/z	Found (%) (Required) C	H	N
5a $C_{20}H_{25}NO_3S$	86.2	73	99.2	−233.3	134.5–135	359/144	66.9 (66.8	7.15 7.0	4.05 3.9)
5b $C_{21}H_{27}NO_4S$	92.1	73	98.8	−180.7	148–148.5	389/174	64.75 (64.8	7.1 7.0	3.6 3.6)
5c $C_{21}H_{27}NO_4S$	72.3	63	97.7	−213.1	180–182	389/147	64.85 (64.8	7.05 7.0	3.6 3.6)
5d $C_{23}H_{31}NO_6S$	66.8	62	97.6	−185.5	158–159	449/207	61.6 (61.45	7.05 6.95	3.0 3.1)
5e $C_{14}N_2O_3S\cdot 1/4H_2O$	59.6	29[f]	96.1[g]	−234.2	171–173	384/170	64.6 (64.8	6.15 6.35	7.15 7.2)
(+)-**5g** $C_{21}H_{26}FNO_4S$	73.4	45	>99.5	+181.4	147.5–150	407/165	61.6 (61.9	6.4 6.4	3.3 3.4)
(−)-**5g** $C_{21}H_{26}FNO_4S$	79.7	46	99.8	−181.4	146–149	407/165	61.9 (61.9	6.4 6.4	3.6 3.4)
(+)-**5h** $C_{24}H_{31}NO_5S$	62.6[h]	11[i]	99.3	+187.0	167–169	445/430	64.75 (64.7	6.95 7.0	3.2 3.1)
(−)-**5h** $C_{24}H_{31}NO_5S$	60.4[h]	18[j]	99.4	−193.7	169.5–170.5	445/430	64.95 (64.7	7.25 7.0	3.55 3.1)
(+)-**5i** $C_{18}H_{23}NO_3S_2$	87.7	71	99.3	+222.4[k]	121–124	365/150	58.8 (59.15	6.35 6.3	3.7 3.8)
(−)-**5i** $C_{18}H_{23}NO_3S_2$	86.5	67	99.4	−218.6[k]	121–124	365/150	58.8 (59.15	6.15 6.3	3.9 3.8)
5k $C_{18}H_{22}BrNO_3S_2$	67.7	59	87.9	−168.9	199–200	445/122	48.8 (48.65	5.15 5.0	3.25 3.15)
5l $C_{18}H_{23}NO_4S\cdot 1/4H_2O$	76.3	67	99.7	−267.5	139–140	349/134	61.0 (61.1	6.6 7.0	3.7 4.0)
5m $C_{24}H_{29}FeNO_3S$	82.3	76	>96.0[l]	−172.2	220–228[m]		61.95 (61.7	6.3 6.25	3.1 3.0)
5n $C_{15}H_{23}NO_3S$	90.8	72	99.4	−120.1	154–155	297/83	60.7 (60.6	7.85 7.8	4.6 4.7)
5o $C_{24}H_{41}NO_3S$	83.2	62[n]	>99.8	−89.0	50–50.5	423/55	68.2 (68.2	9.75 9.5	3.25 3.2)

[a] Determined on the crude product. [b] Yield of recrystallized product. [c] Determined on recrystallized material. [d] *c* 1.0 in CH_2Cl_2. [e] *m/z* of molecular ion and base peak. [f] Only 86% conversion according to GLC-FID. [g] Recrystallized from diethyl ether. [h] Determined by a combination of GLC and ^1H NMR spectroscopy. [i] Only 62% conversion according to ^1H NMR spectroscopy. [j] Only 72% conversion according to ^1H NMR spectroscopy. [k] In acetone. [l] Determined by HPLC (straight phase, hexane with 0.3% of ethanol. Peaks were assigned by derivatizing the racemic cyclopropanecarboxylic acid with camphorsultam and by using the diastereoisomeric mixture as reference). The minor diastereoisomer was not detected. [m] Decomposition. [n] Purified by flash chromatography [SiO_2; diethyl ether–light petroleum (1:4)].

Table 3 Physical and analytical data for cyclopropanecarboxylic acids **6**

Compound	Method	Yield (%)	$[\alpha]_D^{22}$	*c* (solv.)	M.p. (T/°C)
6a $C_{10}H_{10}O_2$	IV	89	−287.2[a]	0.5/EtOH	oil
6b $C_{11}H_{12}O_3$	IV	81	−195.6[b]	1.0/$CHCl_3$	72–73
6c $C_{11}H_{12}O_3$	IV	81	−257.7[c]	0.5/CH_2Cl_2	oil
6m $C_{14}H_{14}FeO_2$	IV	95	−33.0[d]	1.0/C_6H_6	103–106
6n $C_5H_8O_2$	V	63	−96.9[e]	1.0/EtOH	oil

[a] Lit.,[27a] −287.6 (*c* 1.21, EtOH). [b] Lit.,[4a] −196.5 (*c* 0.5, $CHCl_3$), m.p. 74.5–75.5 °C. [c] Lit.,[4a] −304.1 (*c* 1.1, CH_2Cl_2). [d] Lit.,[27b] −26.7 (*c* 0.91, C_6H_6), m.p. 105–120 °C. [e] Lit.,[27a] −71.9 (*c* 1.0, EtOH).

Stereochemistry of the Cyclopropanation.—The optical rotations of the five cyclopropanecarboxylic acids (**6a–c**, **6m** and **6n**) were measured and compared with literature data:[4,27] all five analogues produced data consistent with the 1*R*,2*R* stereochemistry. In addition, an X-ray structure analysis of compound **5m** (see below) unambiguously confirmed the 1*R*,2*R* stereochemistry. This implies that the sultam auxiliary confers the same sense of π-face selectivity in the diazomethane/$Pd(OAc)_2$ cyclopropanation as it does in OsO_4-catalysed dihydroxylations,[13] Pd-catalysed catalytic hydrogenations[14] and in several cycloadditions.[18]

Crystallographic Description of Compound **5m**.—The structure and absolute configuration determinations were carried out as described in the Experimental section. Two crystallographically independent solid-state conformers (the unprimed and primed molecules) were identified in the crystals (Fig. 1). The bond lengths and bond angles in these two molecules are comparable {characteristic mean bond distances are: Fe–C = 2.04[1], C_{sp3}–C_{sp3} = 1.52[3], C_{sp2}–C_{sp2} = 1.41[2], S=O = 1.43[1], C_{sp3}–S = 1.79(1), C_{sp3}–N = 1.48(1), C_{sp2}–N = 1.38(1), N–S = 1.69(1), C=O = 1.21(1) Å; the measure of dispersion around the arithmetic average is given in

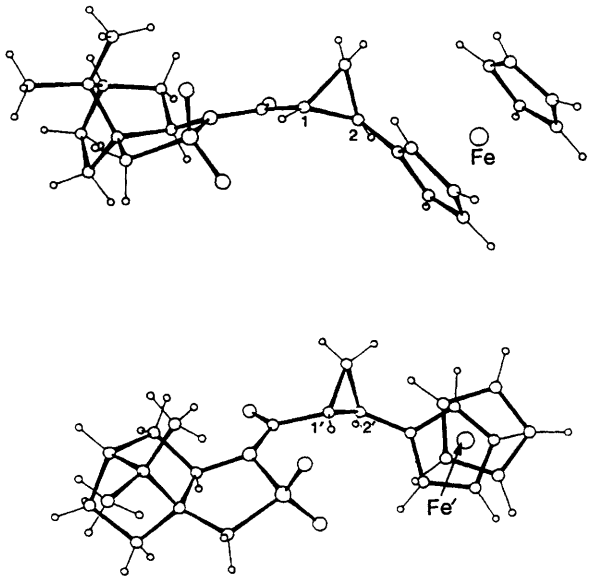


Fig. 1 Perspective views of the two conformers found in the crystal of **5m**

square brackets, where average over more than three values; and ordinary esds are indicated in parenthesis for the others}. The molecular conformations are, however, different (see Supplementary Material); the semirigid-fused ring system of the bornane-10,2-sultam moiety shows similar conformations in the two independent molecules. Generally, the conformation of any non-planar cyclic fragment is characterized either by a description of the deviation from planarity, or by the torsional angles. The ring-puckering parameters, which describe the geometry of the puckering relative to the average ring plane,[28] yielded comparable values for corresponding parameters, except for the two φ angles for the five-membered sultam rings, which differ by ~ 17°. Furthermore, the asymmetry parameters were calculated from symmetry-related torsion angles,[29] which define the conformation of any ring, relative to an ideal conformation (*e.g.*, chair, boat, envelope). A zero value for D_s (= mirror-plane asymmetry parameter), or D_2 (= two-fold asymmetry parameter) means that the symmetry in question is present at the location indicated. In the present case, three out of the four rings of the bornanesultam moiety have practically the same symmetry in the two conformers, because they yielded low (< 0.1) values for identical asymmetry parameters in the two molecules. Nevertheless, the conformational difference between the remaining part of the molecules is pronounced. An analysis of selected torsion angles[30,31] indicated that the direction of the carbonyl group differs somewhat in the two molecules, but that the largest difference is in the orientation of the cyclopropane ring relative to the ferrocene moiety. The least-squares plane of the three-membered ring is approximately perpendicular to the aromatic ring planes in the unprimed conformer, whereas the corresponding dihedral angles in the primed molecule are larger by ~ 40°. The geometries of the ferrocene sandwiches, however, agree well with each other. The mean distance of the Fe^{2+} ion from the aromatic planes is 1.654[5] Å.

Temperature Dependence.—Preliminary experiments indicated that the stereoselectivity of the cyclopropanation was dependent on temperature. Therefore, the influence of the reaction temperature on the stereoselectivity of cyclopropanation of three compounds with differently substituted aryl moieties was studied: compound **4a** has a phenyl substituent, compound **4d** has a phenyl substituent carrying three methoxy groups, and compound **4e** is substituted with a phenyl group carrying a cyano group. With substrates **4a** and **4d**, the cyclopropanation was quantitative at temperatures between −30 and +28 °C. With compound **4e** as a substrate, the reaction became more sluggish, and quantitative conversion was observed only at temperatures between 26 and 35 °C.

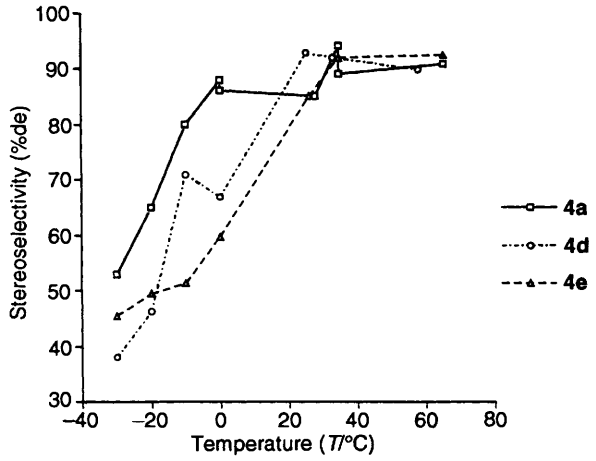
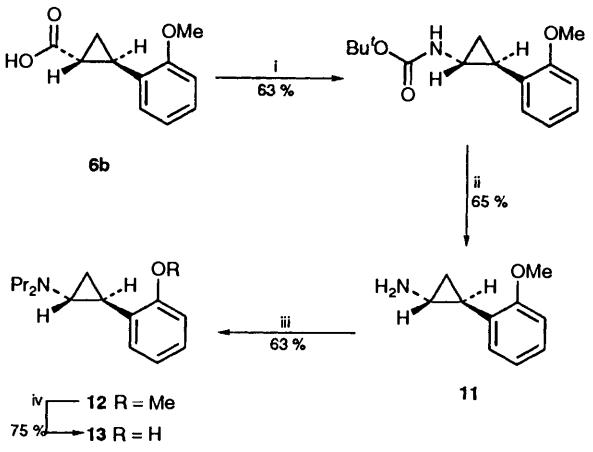


Fig. 2 Effect of reaction temperature on the stereoselectivity of cyclopropanation of compounds **4a**, **4d** and **4e**. At temperatures above 35 °C, diethyl ether and dichloromethane were replaced with THF and 1,2-dichloroethane, respectively.

The stereoselectivity of the reaction, which was studied by GLC analysis of the resulting diastereoisomeric cyclopropanes, increased with temperature regardless of substrate (Fig. 2). All three compounds reached the same maximal level of stereoselectivity, *i.e.* ~ 90% de. However, the maximal stereoselectivity for substrate **4a** was obtained at lower temperatures than was that of substrates **4d** and **4f**. The mechanism of the palladium-catalysed cyclopropanation is not known but these results seem to imply that (a) the stereoselectivity of the reaction is insensitive to the electron distribution in the vinyl group or (b) different mechanistic steps are rate determining in the cyclopropanation of electron-rich and electron-poor enoyl sultams. These conclusions were corroborated by our inability to find any correlation (the correlation coefficient r^2 was consistently smaller than 0.13) between ^{13}C or ^{1}H chemical shifts (or differences in chemial shifts) of the vinyl group and the observed stereoselectivities in Table 2. Therefore, the only trend which appears to be consistent is that enoyl sultams substituted with electron-deficient groups (**4e** and **4f**) react at a slower rate than do other derivatives.

It should be noted that the shape of the temperature curves (Fig. 2) indicates that the cyclopropanation has an isoinversion point and, consequently, that the temperature-dependent stereoselectivity of the reaction may be best described by two independent mechanistic steps: one in which the stereoselectivity is determined by entropy and the other by enthalpy (*cf.* ref. 32).

Concluding Remarks.—The cyclopropanation presented herein provides cyclopropanated derivatives of high diastereoisomeric purity when applied to acryloyl sultams carrying aryl or alkyl substituents in the β-position. Substitution in the α-position of the vinyl group lowers reaction rates, and substitution in the β-position with electron-withdrawing groups appears to be particularly unfavourable. In general, the overall bulk of the sultam moiety appears to decrease reaction rates. The usefulness of the reaction was demonstrated by a stereoselective synthesis of the interesting 5-HT_{1A}-receptor agonist **13**[4a] (Scheme 4).



Scheme 4 *Reagents and conditions:* (i) EtOCOCl; then NaN_3, 90 °C; then Bu'OH; (ii) HCl; (iii), (iv) see ref. 4*a*

Experimental

^1H NMR and ^{13}C NMR spectra were recorded on JEOL JNM-EX270 and JEOL FX 90Q spectrometers. Coupling constants (*J*) are given in Hz. GLC-analysis was performed on a Shimadzu GC-14A equipped with an FID detector and an HP1 column (50 m × 0.32 mm). Assignment of the peak identity with GLC-MS was made on a Hewlett-Packard mass spectrometer HP 5971A MSD connected to a gas chromatograph HP GC 5890 Series 2, equipped with an HP1 column (25 m × 0.2 mm). Fast-atom bombardment (FAB) was performed by using a Finnigan-MAT 95 double-focussing mass spectrometer. The instrument was operated at full accelerating voltage of 4.7 kV, a resolution of approximately 1200, and a scan speed of 5s per decade. The scan range was 150–500 amu. The FAB gun (Ion Tech) operated at 8 kV with xenon gas to give a monitor of ~40 μA. The sample was dissolved in CH_2Cl_2. Glycerol was used as matrix on a stainless steel probe tip. M.p.s. (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. The elemental analyses (C, H and N) were performed by Micro Kemi AB, Uppsala, Sweden. TLC was carried out on aluminium sheets precoated with silica gel F_{254} (0.2 mm) and visualized with UV light and/or I_2 except where noted. All reactions except the cyclopropanations were performed under N_2. Light petroleum refers to the fraction boiling in the range 40–65 °C.

Methyl (E)-3-(2-*Acetylphenyl*)*propenoate*.—A mixture of 2′-bromoacetophenone (4.0 cm^3, 30 mmol), methyl acrylate (4.0 cm^3, 44 mmol), triethylamine (20 cm^3), $Pd(OAc)_2$ (0.13 g, 0.59 mmol) and tri-*o*-tolylphosphine (0.72 g, 2.4 mmol) was heated at 100 °C in a sealed flask for 24 h. The resulting mixture was concentrated and the residue was partitioned between Et_2O (100 cm^3) and 1 mol dm^{-3} HCl (3 × 50 cm^3). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography [Et_2O–light petroleum (1:2)] to afford the *desired ester* (5.3 g, 88%), m.p. 45–46 °C (Found: C, 70.3; H, 5.9. $C_{12}H_{12}O_3$ requires C, 70.6; H, 5.9%); δ_H(90 MHz; $CDCl_3$; Me_4Si) 2.6 (3 H, s), 3.8 (3 H, s), 6.3 (1 H, d, *J* 15.9), 7.4–7.8 (4 H, m) and 8.2 (1 H, d, *J* 15.9); δ_C(22.5 MHz; $CDCl_3$; Me_4Si) 29.1, 51.6, 120.3, 128.3, 129.4, 129.5, 132.0, 134.6, 138.1, 144.3, 166.8 and 200.7.

Methyl (E)-3-[2-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)*phenyl*]*propenoate*.—A mixture of methyl (*E*)-3-(2-acetylphenyl)propenoate (3.8 g, 19 mmol), ethane-1,2-diol (2.6 cm^3, 4.7 mmol), a catalytic amount of toluene-4-sulfonic acid and benzene (100 cm^3) was heated to reflux in a Dean–Stark apparatus for 14 h. The mixture was washed with 5% aq. $NaHCO_3$ (3 × 50 cm^3), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography [Et_2O–light petroleum (1:3)] to afford the *desired ketal* (4.3 g, 93%) (Found: C, 67.4; H, 6.4. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%); m.p. 88.5–89.5 °C; δ_H(270 MHz; $CDCl_3$; Me_4Si) 1.62 (3 H, s), 3.6–3.7 (2 H, m), 3.7 (3 H, s), 3.9–4.0 (2 H, m), 6.2 (1 H, d, *J* 15.9), 7.2–7.3 (2 H, m), 7.5–7.6 (2 H, m) and 8.5 (1 H, d, *J* 15.9); δ_C(67.8 MHz; $CDCl_3$; Me_4Si) 27.8, 51.6, 64.2 (2 C), 108.8, 119.0, 126.3, 127.8, 128.3, 129.5, 132.8, 141.9, 144.6 and 167.3.

(E)-3-[2-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)*phenyl*]*propenoic Acid* **2**.—A mixture of methyl 3-[2-(2-methyl-1,3-dioxolan-2-yl)-phenyl]propenoate (5.05 g, 20 mmol), 1 mol dm^{-3} NaOH (100 cm^3), MeOH (120 cm^3) and THF (100 cm^3) was stirred at room temperature for 2 h. The resulting mixture was concentrated and the residual aqueous solution was carefully acidified with 1 mol dm^{-3} HCl under constant mixing with CH_2Cl_2 (4 × 100 cm^3). The organic layer was collected, dried (Na_2SO_4), filtered, and concentrated to afford pure *acid* **2** (4.65 g, 98%) (Found: C, 66.3; H, 6.0. $C_{13}H_{14}O_4$ requires C, 66.7; H, 6.0%); m.p. 201.5–203 °C; δ_H[270 MHz; $(CD_3)_2SO$; Me_4Si] 1.6 (3 H, s), 3.6–3.7 (2 H, m), 3.9–4.1 (2 H, m), 6.3 (1 H, d, *J* 15.9), 7.3–7.4 (2 H, m), 7.5–7.6 (1 H, m), 7.7–7.8 (1 H, m) and 8.4 (1 H, d, *J* 15.9); δ_C[67.8 MHz; $(CD_3)_2SO$; Me_4Si] 27.7, 63.9 (2 C), 108.1, 120.1, 125.8, 127.8, 128.5, 129.6, 132.1, 141.5, 143.1 and 167.6.

5-*Fluoro*-2-*methoxybenzaldehyde*.—4-Fluoroanisole (2.0 cm^3, 18 mmol), dimethoxymethane (5.6 cm^3, 63 mmol), conc. HCl (35 cm^3) and conc. H_2SO_4 (0.9 cm^3) were mixed at 70 °C for 3 h and was then cooled to room temperature. Water (80 cm^3) was added and the mixture was extracted with Et_2O (3 × 40 cm^3). The combined organic layers were washed with water (2 × 30 cm^3), dried (Na_2SO_4), filtered, and concentrated to afford crude 2-chloromethyl-4-fluoroanisole (3.0 g), which was mixed with hexamethylenetetramine (4.83 g, 35 mmol) and 50% aq. HOAc (15 cm^3). This mixture was heated to reflux for 2 h and conc. HCl (6 cm^3) was added. The heating was discontinued after 15 min and the cooled reaction mixture was extracted with Et_2O (10 cm^3). The organic layer was washed with water (3 × 5 cm^3) and 40% aq. Na_2CO_3 (1 × 5 cm^3), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography [Et_2O–light petroleum (1:8)] to afford the desired aldehyde (1.46 g, 54%), m.p. 43–45.5 °C (lit.,[21] 43 °C), δ_H(90 MHz; $CDCl_3$; Me_4Si) 3.9 (3 H, s), 6.9–7.0 (1 H, m), 7.1–7.5 (1 H, m), 7.5–7.6 (1 H, m) and 10.4 (1 H, d, *J* 3.1); δ_C(22.5 MHz; $CDCl_3$; Me_4Si) 56.2, 113.2 (d, *J* 7.0), 113.9 (d, *J* 23.7), 122.5 (d, *J* 23.7), 125.4 (d, *J* 6.3), 156.9 (d, *J* 240.8), 158.2 (d, *J* 2.1) and 188.7 (d, *J* 1.4).

(E)-3-(5-*Fluoro*-2-*methoxyphenyl*)*propenoic Acid* **3**.—A mixture of 5-fluoro-2-methoxybenzaldehyde (6.5 g, 42.2 mmol), malonic acid (9.8 g, 94 mmol), piperidine (0.7 cm^3, 7.1 mmol) and pyridine (31 cm^3) was stirred at room temperature for 16 h. The temperature was raised to 60 °C (bath temperature) and after 4 h the temperature was increased to 100 °C until the evolution of CO_2 had ceased (3 h). After cooling, the solution was poured into a mixture of water (400 cm^3), conc. HCl (46 cm^3) and ice. The precipitated carboxylic acid was collected by filtration, washed with water until the filtrate had approximately neutral pH (pH paper), and dried to afford *compound* **3** (8.01 g, 96.6%) as a solid, m.p. 209–210 °C (Found: C, 61.2; H, 4.7. $C_{10}H_9FO_3$ requires C, 61,2; H, 4.6%); δ_H(270 MHz; [$^2H_6$]acetone; Me_4Si) 3.9 (3 H, s), 6.6 (1 H, d, *J* 16.2), 7.1–7.6

(3 H, m) and 8.0 (1 H, dd, *J* 16.2 and 1.3); δ_C(22.5 MHz; [$^2H_6$]acetone; Me_4Si) 56.6, 113.7 (d, *J* 7.3), 115.0 (d, *J* 24.4), 118.5 (d, *J* 23.2), 120.8, 125.3 (d, *J* 8.5), 139.1 (d, *J* 2.4), 155.5 (d, *J* 1.8), 157.8 (d, *J* 236.8) and 168.0.

(2'R)-N-[(E)-*cinnamoyl*]*bornane*-10',2'-*sultam* **4a**. *Method I.*—A solution of (2*R*)-borane-10,2-sultam **1** (0.80 g, 3.7 mmol) in dry toluene (25 cm^3) was added to a stirred mixture of NaH (0.12 g, 5.1 mmol; 80% in mineral oil) in dry toluene (20 cm^3). The mixture was stirred for 30 min. A solution of cinnamoyl chloride [prepared by stirring of cinnamic acid (0.50 g, 3.4 mmol) in $SOCl_2$ (5 cm^3) for 2 h at room temperature followed by concentration of the mixture under reduced pressure, addition of CH_2Cl_2, and cor---tration, the last steps repeated twice] in dry toluene (25) was added slowly and the mixture was stirred overnight. Water (20 cm^3) was added and the organic layer was washed successively with water (20 cm^3) and brine (20 cm^3), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude enoyl sultam was recrystallized from EtOH to yield pure compound **4a** (0.96 g), δ_H(270 MHz; $CDCl_3$; Me_4Si) 1.0 (3 H, s), 1.2 (3 H, s), 1.3–1.5 (2 H, m), 1.8–2.2 (5 H, m), 3.4–3.6 [2 H, 2 d, (AB)], 4.0 (1 H, dd, *J* 5.3 and 7.3), 7.2 (1 H, d, *J* 15.5), 7.3–7.4 (3 H, m), 7.5–7.6 (2 H, m) and 7.8 (1 H, d, *J* 15.5); δ_C(22.5 MHz; $CDCl_3$; Me_4Si) 19.8, 20.8, 26.4, 32.7, 38.4, 44.6, 47.7, 48.5, 53.0, 65.1, 117.4, 128.5 (2 C), 128.7 (2 C), 130.5, 134.2, 145.5 and 164.1.

(2'R)-N-[(E)-3-*Ferrocenylprop*-2-*enoyl*]*bornane*-10',2'-*sultam* **4m**. *Method II.*—Compound **4m** was prepared from (2*R*)-bornane-10,2-sultam **1** (0.76 g, 3.5 mmol), toluene (35 cm^3), NaH (0.21 g, 7.0 mmol), and 3-(ferrocenyl)acrylic acid (0.90 g, 3.5 mmol) as described above with the difference that the acid chloride was prepared by stirring of the acid with toluene (30 cm^3) and oxalyl dichloride (0.60 cm^3, 7.0 mmol) at 50 °C for 5 h. The yield of product **4m** was 1.31 g; δ_H(270 MHz; $CDCl_3$; Me_4Si) 1.0 (3 H, s), 1.2 (3 H, s), 1.3–1.4 (2 H, m), 1.8–2.0 (3 H, m), 2.1–2.2 (2 H, m), 3.4–3.6 [2 H, 2 d, (AB)], 4.0 (1 H dd, *J* 5.1 and 7.5), 4.2 (5 H, s), 4.4 (2 H, br s), 4.5 (1 H, br s), 4.6 (1 H, br s), 6.7 (1 H, d, *J* 15.0) and 7.7 (1 H, d, *J* 15.0); δ_C(22.5 MHz; $CDCl_3$; Me_4Si) 19.9, 20.8, 26.5, 32.8, 38.5, 44.7, 47.7, 48.3, 53.1, 65.1, 69.0, 69.1, 69.8 (5 C), 71.16, 71.25, 78.3, 114.3, 147.0 and 164.4.

(2'R)-N-[(E)-*cinnamoyl*]*bornane*-10',2'-*sultam* **4a**. *Method V.*—A mixture of compound **4x** (0.10 g, 0.46 mmol), tetrabutylammonium chloride (TBACl) monohydrate (0.14 g, 0.46 mmol), $Pd(OAc)_2$ (0.002 g, 9 μmol), K_2CO_3 (0.16 g, 1.2 mmol) and iodobenzene (0.05 cm^3, 0.5 mmol) in dimethylformamide (DMF) (1 cm^3) was stirred at room temperature for 24 h. The crude mixture was partitioned between EtO_2 and water and the organic layer was washed four times with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography [$CHCl_3$–light petroleum (4:1)] to afford pure compound **4a** (0.09 g, 56%).

(2'R)-N-[(E)-2-*Phenylcyclopropanecarbonyl*]*bornane*-10',2'-*sultam* **5a**. *Method III.*—Diazomethane (**CAUTION**[33]) was prepared as previously described;[33] a solution of *N*-methyl-*N*-nitrosotoluene-4-sulfonamide (Diazogen™) (6.47 g, 30.2 mmol) in Et_2O (225 cm^3) was slowly added to a heated (70 °C, bath temperature) mixture of KOH (5.1 g, 87 mmol), Et_2O (10 cm^3), water (30 cm^3), and 2-(2-ethoxyethoxy)ethanol (30 cm^3). The solution of diazomethane thus formed was continuously distilled into a stirred, cooled (ice-bath) solution of compound **4a** (1.04 g, 3.01 mmol) and $Pd(OAc)_2$ (3.4 mg, 15 μmol) in CH_2Cl_2 (70 cm^3). The reaction was quenched by addition of a few drops of HOAc after 3 h. The mixture was washed with aq. 5% $NaHCO_3$ (25 cm^3), dried ($MgSO_4$), and filtered through a 2 cm long silica column (eluted with CH_2Cl_2). The filtrate was analysed by GLC to determine the diastereoisomeric excess of the crude product. The solution was concentrated under reduced pressure and the residue was recrystallized from EtOH to yield pure (99.2% de) title compound **5a** (0.79 g), δ_H(270 MHz; $CDCl_3$; Me_4Si) 1.0 (3 H, s), 1.2 (3 H, s), 1.3–1.4 (3 H, m), 2.2–1.7 (6 H, m), 2.5–2.6 (2 H, m), 3.4–3.6 [2 H, 2 d, (AB)], 3.9–4.0 (1 H, m) and 7.2–7.4 (5 H, m); δ_C(22.5 MHz; $CDCl_3$; Me_4Si) 17.2, 19.8, 20.8, 24.1, 26.4, 28.5, 32.7, 38.5, 44.7, 47.7, 48.4, 53.0, 65.3, 126.5, 127.0 (2 C), 128.3 (2 C), 139.4 and 171.2.

(2'R,4S)-N-[4,5-*Dihydro*-4-*methyl*-4-(*trifluoromethyl*)-3-*carbonyl*]*bornane*-10',2'-*sultam* **10**.—Compound **4u** (0.42 g, 1.2 mmol) was treated with diazomethane as described above to yield a complex product mixture. The crude product was purified by flash chromatography [Et_2O–light petroleum (4:1)]. Recrystallization from EtOH gave *title compound* **10** (0.030 g, 6%), m.p. 224–226 °C; $[\alpha]_D^{22}$ −45.5 (*c* 0.275, $CHCl_3$) (Found: C, 48.1; H, 5.8; N, 9.95. $C_{16}H_{22}F_3N_3O_3S{\cdot}H_2O$ requires C, 47.75; H, 5.8; N, 10.4%); δ_H(270 MHz; $CDCl_3$; Me_4Si) 1.0 (3 H, s), 1.2 (3 H, s), 1.3–1.5 (2 H, m), 1.7 (3 H, s), 1.8–2.0 (4 H, m), 3.3–3.5 (3 H, m), 4.0 (1 H, d, *J* 10.9), 4.2 (2 H, dd, *J* 6.1 and 6.1) and 6.8 (1 H, br s, D_2O-exch); δ_C(67.8 MHz; $CDCl_3$; Me_4Si) 18.8, 20.0, 21.7, 26.3, 33.5, 39.1, 45.6, 47.7, 48.3, 53.4, 55.7 (q, *J* 29.3), 57.6, 66.4, 126.4 (q, *J* 282), 139.3 and 161.7; FAB-MS: *m/z* 394 (M + 1, 24%), 277 (13) and 185 (100).

(1R,2R)-2-(3-*Methoxyphenyl*)*cyclopropanecarboxylic Acid* **6c**. *Method IV.*—Titanium(IV) isopropoxide (0.23 cm^3, 1.0 mmol) was added to a solution of sultam **5c** (0.30 g, 1.0 mmol) in benzyl alcohol (1 cm^3). The solution was heated at 150 °C for 30 min. The crude reaction mixture was purified directly on a silica gel column eluted with Et_2O–light petroleum (1:8) to yield a mixture (0.20 g) of the benzyl and isopropyl esters. The ester mixture was dissolved in THF (5 cm^3), MeOH (5 cm^3), and aq. 2 mol dm^{-3} NaOH (5 cm^3), and stirred for 2 h. The mixture was concentrated and the remaining alkaline solution was washed with Et_2O (4 × 15 cm^3), acidified with aq. 5 mol dm^{-3} HCl, extracted with CH_2Cl_2 (4 × 10 cm^3), and the extracts were dried ($MgSO_4$), filtered, and concentrated to yield the pure acid **6c** (0.12 g), δ_H(270 MHz; $CDCl_3$; Me_4Si) 1.4 (1 H, ddd, *J* 4.7, 6.6 and 8.4), 1.6 (1 H, ddd, *J* 4.4, 4.7 and 9.4), 1.9 (1 H, ddd, *J* 4.3, 4.4 and 8.4), 2.6 (1 H, ddd, *J* 4.3, 6.6 and 9.4), 3.8 (3 H, s), 6.8–6.9 (3 H, m) and 7.3–7.1 (1 H, m); δ_C(67.8 MHz; $CDCl_3$; Me_4Si) 17.5, 24.0, 27.1, 55.2, 112.0, 112.2, 118.5, 129.6, 141.2, 159.7 and 179.8.

(1R,2R)-2-*Methylcyclopropanecarboxylic Acid* **6n**. *Method V.*—A mixture of sultam **5n** (0.20 g, 0.67 mmol), $LiOH{\cdot}H_2O$ (0.28 g, 6.7 mmol), THF (8 cm^3) and water (0.2 cm^3) was stirred for 6 days at 50 °C. The mixture was concentrated and the residue was dissolved in water (10 cm^3). The alkaline solution was washed with Et_2O (10 cm^3), acidified with aq. 5 mol dm^{-3} HCl, and extracted with Et_2O (4 × 10 cm^3), and the extract was dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography [$CHCl_3$–MeOH (19:1)] to afford pure title compound **6n** (42 mg) which was visualized on TLC with 2,6-dichlorophenol–indophenol sodium salt;[34] δ_H(270 MHz; $CDCl_3$; Me_4Si) 0.75 (1 H, ddd, *J* 6.5, 8.2 and 4.1), 1.12 (3 H, d, *J* 6.0), 1.23 (1 H, ddd, *J* 4.1, 8.6 and 4.3), 1.32 (1 H, ddd, *J* 8.2, 4.1 and 4.3), 1.45 (1 H, dddd, *J* 6.5, 4.1, 8.6 and 6.0) and 10.3 (1 H, br s); δ_C(22.5 MHz; $CDCl_3$; Me_4Si) 17.6, 17.8, 18.3, 21.2 and 181.3.

(1R,2S)-2-(2-*Methoxyphenyl*)*cyclopropylamine* **11**.—Ethyl chloroformate (3.0 cm^3, 31 mmol) was added to a stirred, cooled (−10 °C) solution of the acid **6b** (4.0 g, 21 mmol) and

triethylamine (3.8 cm^3, 27 mmol) in dry acetone (150 cm^3). After 2 h, aq. NaN_3 (2.18 g, 34 mmol in 6.5 cm^3) was added and the mixture was stirred for one additional hour. Water (50 cm^3) was added and the solution was concentrated under reduced pressure. The residue was extracted with Et_2O (4 × 70 cm^3). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude acyl azide thus obtained was dissolved in dry toluene (200 cm^3). The resulting solution was concentrated to ~two-thirds of the original volume and was heated to 90 °C (bath temperature) for 3 h. The mixture was concentrated and the residue was dissolved in dry *tert*-butyl alcohol (150 cm^3) and heated to reflux for 16 h. The mixture was concentrated and the crude carbamate was purified by flash chromatography [Et_2O–light petroleum (1:4)]. The *tert*-butyl carbamate was dissolved in *tert*-butyl alcohol (50 cm^3)–aq. 1 mol dm^{-3} HCl (200 cm^3). The mixture was heated at 100 °C (bath temperature) for 20 min. The resulting solution was concentrated and the acidic aqueous solution was washed with Et_2O (100 cm^3), alkalinized by addition of Na_2CO_3(s), and extracted with Et_2O (4 × 100 cm^3). The latter organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in Et_2O and treated with ethereal HCl. The precipitate was recrystallized from MeCN–EtOH to yield pure amine **11**·HCl (1.69 g, 41%), m.p. 217–220 °C (decomp.) (lit.,[4a] 215–217.5 °C); $[\alpha]_D^{22}$ −44.2 (*c* 1.6, MeOH) [lit.,[4a] −43.7 (*c* 1.6, MeOH)]; δ_H(270 MHz; CD_3OD; Me_4Si) 1.2–1.3 (1 H, m), 2.4 (1 H, ddd, *J* 3.6, 7.4 and 9.8), 2.6 (1 H, ddd, *J* 3.6, 4.5 and 7.3), 3.9 (3 H, s), 6.7–6.9 (3 H, m) and 7.1–7.2 (1 H, m); δ_C(22.5 MHz; CD_3OD; Me_4Si) 11.8, 17.4, 30.8, 55.5, 111.0, 121.1, 127.0 (2 C), 128.6 and 159.1.

Methyl (E)-3-[2-(*Trifluoromethyl*)*phenyl*]*propenoate* **7**.—A mixture of 2-iodo-1-(trifluoromethyl)benzene (5.5 cm^3, 39.2 mmol), methyl acrylate (5.5 cm^3, 60.7 mmol), TBACl monohydrate (10.9 g, 36.8 mmol), $Pd(OAc)_2$ (0.18 g, 0.78 mmol) and K_2CO_3 (13.5 g, 98.0 mmol) in DMF (50 cm^3) was stirred for three days at room temperature. The reaction mixture was poured into brine (100 cm^3)–light petroleum (100 cm^3). This mixture was filtered (Celite) and the phases were separated. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by distillation (66–68 °C; 0.01 mmHg) to afford *title compound* **7** (7.02 g, 78%) as an oil (Found: C, 57.1: H, 4.0. $C_{11}H_9F_3O_2$ requires C, 57.4; H, 3.9%); δ_H(90 MHz; $CDCl_3$; Me_4Si) 3.8 (3 H, s), 6.4 (1 H, d, *J* 15.8), 7.4–7.8 (4 H, m) and 8.1 (1 H, dq, *J* 2.1 and 15.8); δ_C(22.5 MHz; $CDCl_3$; Me_4Si) 51.9, 122.2, 124.1 (q, *J* 273), 126.2 (q, *J* 5.6), 128.0 (2 C), 129.7 (2 C), 132.2, 140.3 (q, *J* 2.1) and 166.6.

(1R*,2R*)-2-[2-(*Trifluoromethyl*)*cyclopropanecarboxylic Acid*.—Methyl (*E*)-3-[2-(trifluoromethyl)phenyl]acrylate (6.5 g, 28 mmol) was cyclopropanated as described above at −10 °C. The crude ester, which showed no contamination of remaining substrate, was purified by flash chromatography [Et_2O–light petroleum (1:4)]. The intermediate cyclopropanecarboxylic ester was dissolved in a mixture of MeOH (90 cm^3) and 2 mol dm^{-3} aq. NaOH (90 cm^3). The mixture was stirred at room temperature for 1.5 h and was then concentrated. The remaining alkaline aqueous layer was washed with Et_2O (30 cm^3), acidified with 5 mol dm^{-3} HCl, extracted with Et_2O (3 × 40 cm^3), dried ($MgSO_4$), and concentrated. The crude acid was recrystallized from Et_2O to afford the pure *acid* (3.64 g, 69%) m.p. 117–118.5 °C (Found: C, 57.0; H, 3.9. $C_{11}H_9F_3O_2$ requires C, 57.4; H, 3.9%); δ_H(270 MHz; $CDCl_3$; Me_4Si) 1.4–1.5 (1 H, m), 1.7 (1 H, ddd, *J* 4.8, 4.8 and 9.3), 1.9 (1 H, ddd, *J* 4.5, 4.5 and 9.3), 2.4 (1 H, br s), 2.8–2.9 (1 H, m), 7.2 (1 H, d, *J* 7.9), 7.3 (1 H, dd, *J* 7.0 and 7.6), 7.5 (1 H, dd, *J* 7.6 and 7.3) and 7.7 (1 H, d, *J* 7.3); δ_C(22.5 MHz; CD_3OD; Me_4Si) 16.0, 23.9, 24.8, 126.0 (q, *J* 273), 126.9 (q, *J* 5.8), 127.9 (2 C), 128.0, 133.4, 139.4 and 176.6.

Methyl (1R*,2R*)-1,2-*Dimethylcyclopropanecarboxylate*.—Diazomethane, generated as described above from Diazogen (5.35 g, 25.0 mmol), KOH (4.2 g, 75 mmol), water (50 cm^3), 2-(2-ethoxyethoxy)ethanol (50 cm^3) and Et_2O (300 cm^3), was distilled into a cooled (0 °C) solution of (*E*)-1,2-dimethylacrylic acid (0.31 g, 3.1 mmol) in CH_2Cl_2 (50 cm^3). A solution of $Pd(OAc)_2$ (2.8 mg, 0.12 mmol) in CH_2Cl_2 was added when the mixture showed some remaining yellow colour, indicating that all acid had been converted into the corresponding methyl ester. The reaction was quenched by addition of a few drops of HOAc after 3 h. The solution was washed with 5% aq. $NaHCO_3$ (25 cm^3), dried ($MgSO_4$), and filtered through a 2 cm long silica column (eluted with CH_2Cl_2). GLC analysis indicated a 13:87 relation between the unsaturated methyl ester and the cyclopropanated product. The peak identities were confirmed by GLC-MS analysis.

Some Additional Cyclopropanations.—Compounds **4f** (de = 68%, 50% conv., GLC-MS only, *m/z* 427, 44), **4q** (de = 51%, 15% conv., *m/z* 311, 97), and **4r** (de = 97.4%, 32% conv., *m/z* 311, 218) did not undergo complete conversion into the cyclopropanated product and we were not able to isolate the pure product. Consequently the diastereoselectivity of the reaction with these compounds was analysed on GLC-MS and GLC-flame ionization detection only. The crude product from the cyclopropanation of the conjugated diene **4p** contained the dicyclopropanated (75% de = 87.3%, *m/z* 337, 135) and both the monocyclopropanated products (8% de = 80.1%, *m/z* 323, 108; and 17% only one peak, *m/z* 323, 109).

(1R,2S)-2-(2-*Methoxyphenyl*)-N,N-*dipropylcyclopropylamine* **12** *and* (1R,2S)-2-(2-*Hydroxyphenyl*)-N,N-*dipropylcyclopropylamine** **13**.—These compounds were prepared as previously described.[4a] Compound **12**·HCl (1.64 g, 82%), m.p. 175–178 °C (decomp.) (lit.,[4a] 174–175.5 °C); $[\alpha]_D^{22}$ −9.77 (*c* 1.3, MeOH) [lit.,[4a] − 10.0 (*c* 1.3, MeOH)]; δ_H(270 MHz; CD_3OD; Me_4Si) 0.9 (6 H, dd, *J* 7.4 and 7.4), 1.5–1.6 (2 H, m), 1.7–1.8 (4 H, m) 2.6–2.7 (1 H, m), 2.7–2.9 (1 H, m), 3.2–3.4 (4 H, m), 2.7–2.9 (1 H, m), 3.2–3.4 (4 H, m), 3.8 (3 H, s), 6.8–6.9 (3 H, m) and 7.1–7.4 (1 H, m); δ_C(22.5 MHz; CD_3OD; Me_4Si) 11.4, 12.3, 18.4, 18.7, 46.0, 55.9, 57.7, 111.5, 121.8, 126.4, 127.5, 129.5 and 159.6; compound **13**·HBr (0.17 g, 77%), m.p. 202–204 °C (lit.,[4a] 197–198 °C); $[\alpha]_D^{22}$ −7.2 (*c* 1.1, MeOH) [lit.,[4a] −7.1 (*c* 1.1, MeOH)]; δ_H(270 MHz; CD_3OD; Me_4Si) 1.0 (6 H, dd, *J* 7.4 and 7.4) 1.5–1.6 (2 H, m), 1.8–1.9 (4 H, m), 2.6–2.7 (1 H, m), 2.8–2.9 (1 H, m), 3.2–3.4 (4 H, m), 6.7–6.8 (2 H, m), 6.9 (1 H, m) and 7.0–7.1 (1 H, m); δ_C(22.5 MHz; CD_3OD; Me_4Si) 11.3, 12.2, 18.4, 18.9, 45.9, 57.7, 115.7, 120.6, 124.6, 127.8, 129.2 and 157.5.

X-Ray Crystallography.—*Data collection and processing*. The yellow, flat-needle-shaped single crystal of compound **5m** [$C_{24}H_{29}FeNO_3S$, M = 467.40, monoclinic ($P2_1$), a = 7.762(1), b = 14833(1), c = 19.140(2) Å, β = 98.07(1)°, V_c = 2181.8(3) $Å^3$, Z = 4, D_c = 1.423 g cm^{-3}, F(000) = 984, μ(Mo-Kα) = 8.1 cm^{-1}], selected for X-ray study, had the approximate dimensions 0.06 × 0.18 × 0.50 mm. The unit-cell dimensions were refined against θ-values of 47 carefully centred reflections with $10.5 < 2\theta < 23.5°$. The intensities of 5570 reflections were measured on an STOE/AED2 automatic diffractometer at room temperature (291 K), using graphite-monochromatized Mo-Kα radiation (λ = 0.710 69 Å, $2\theta_{max}$ =

* 2-[2-(Dipropylamino)cyclopropyl]phenol.

55°) and $\omega/2\theta$ scan technique. Data reduction included corrections for Lorentz, polarization and absorption effects. The absorption corrections were carried out by numerical integration, using the program STOEABS.[35] The transmission factor varied between 0.86 and 0.96. It is noteworthy that more than 60% of the collected reflections had $I/\sigma(I) < 2$, indicating modest scattering ability for the crystal of **5m**.

Structure analysis and refinement. A combination of heavy atom and direct methods, according to the program DIRDIF,[36] yielded a preliminary model comprising reliable positions for all but one of the non-hydrogen atoms in the two crystallographically independent molecules. The structure was completed and refined with different versions of the SHELX program system.[37,38] The non-hydrogen-atom positions were refined together with their anisotropic displacement parameters, whereas the hydrogen atoms were assumed to be in geometrically idealized positions with C–H = 1.00 Å, recalculated after each refining cycle, and a single vibrational parameter was refined from them. The methyl groups were treated as rigid. Only 1859 reflections of the 5186 unique non-zero observations had $I > 2\sigma(I)$ and were used in the refinement calculations based on F. Therefore, at the last stage of the refinement of the 'blocked full-matrix least-squares' technique[38] had to be used, in which the two conformers, with 277 and 278 variables, respectively, were refined in consecutive cycles.

The molecule **5m** possesses five stereogenic centres (see Fig. 1), and the crystal contains this compound in optically pure form. In order to choose between the two possible mirror-symmetry-related stereoisomers, the last refinement calculation was carried out for both enantiomers. Refinement of the model with 1*R* configuration yielded $R\ [= \Sigma|\Delta F|/\Sigma F_o|] = 0.037$ and $wR[= (\Sigma w|\Delta F|^2/\Sigma w|F_o|^2)^{1/2}] = 0.034$, whereas the calculations for the enantiomer with the opposite, 1*S*, configuration converged to $R = 0.039$ and $wR = 0.036$. The weights of the structure factors were assumed[37,38] to be $w = [\sigma^2(F) + 0.000\,35F^2]^{-1}$. The wR_{tot}-values, calculated for the final models, as above, and using all 5186 unique reflections, were 0.052 and 0.053, respectively. We may conclude from these significant differences between corresponding *R*-values, that the studied molecule of compound **5m** has the 1*R* configuration, as shown in Fig. 1.* It was also confirmed by statistical tests on the crystallographic *wR*-values, following both Hamilton[39] and Rogers.[40] Accordingly, the structural model with the opposite 1*S* configuration can be rejected at a significance level of $\alpha \ll 10^{-10}$. Hence Table 5 in the Supplementary Material lists the refined atomic co-ordinates of the correct enantiomer with 1*R*,2*R* configuration for both independent molecules in the crystal. The maximum and minimum values of $\Delta\rho$ in the final difference Fourier map were 0.11 and −0.11 e/Å^{-3}, respectively.

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* Supplementary data (see Instructions for Authors, January issue). One figure describing the numbering used for the X-ray crystallographic analysis and selected conformational features and torsion angles of two solid-state conformers of compound **5m** (Table 4). Fractional atomic co-ordinates of the non-hydrogen atoms (Table 5), bond lengths and bond angles involving the non-hydrogen atoms (Tables 6 and 7), fractional atomic co-ordinates of the hydrogen atoms (Table 8), and list of possible C–H · · · O-type interactions (Table 9) have been deposited as supplementary data at the Cambridge Crystallographic Data Centre. Lists of anisotropic displacement parameters for the non-hydrogen atoms (Table 10) and of the observed and calculated structure factors are available directly from the authors (I. C.).

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