Synthesis of Highly Functionalized, Enantiomerically and Diastereomerically Pure Cyclohexane Derivates via Michael Addition of Chiral 3-Tosyl-2-(2-oxoalkyl)-1,3-oxazolidines and Methyl Vinyl Ketone

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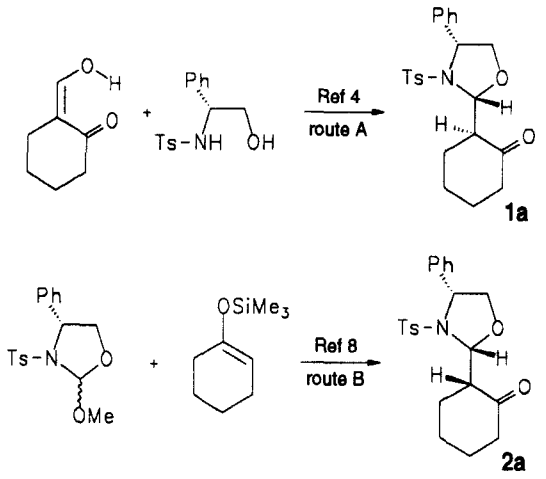
Dedicated to Professor Wolfgang Lüttke on the occasion of his 75th birthday.

Abstract: 2-(2-Oxocycloalkyl)- or 2-phenylacyl-3-tosyl-1,3-oxazolidines **1**, **2**, **9**, and **10** undergo with 3-buten-2-one highly diastereoselective Michael additions under the influence of cesium carbonate to yield 1,5-diketones **8** or **11**, respectively. Intramolecular aldolization of diketones **8** yields stereohomogeneous cyclohexanones **13** or **14**. Addition of nucleophiles to ketones **14**, again, proceeds highly stereoselectively to give diols **17**. Overall, under the stereodirecting influence of *N*-tosyl-2-aminoalkanols, stereohomogeneous protected carbaldehydes are constructed within a few steps from simple achiral precursors.

3-Alkyl-,[1] 3-acyl-,[2] and 3-alkoxycarbonyl-1,3-oxazolidines,[3] derived from enantiomerically pure ß-aminoalkanols, have found various applications in asymmetric synthesis. Recently, we[4] and Scolastico et al.[5] introduced 2-arenesulfonyl-1,3-oxazolidines of type **1** for this purpose.[6] These compounds offer several advantages: As outlined for the epimeric cyclohexanone derivatives **1a** and **2a** (Scheme 1), stereohomogeneous ketones are obtained either by condensation of *N*-tosyl-2-aminoalkanols and 2-(hydroxymethylene)cycloalkanones[2,7] (route A) or from the reaction of 2-alkoxy-3-tosyl-1,3-oxazolidines[8,9,10] with silyl enol ethers[11] (route B). Opposite diastereotopic faces in the ketones **1a** and **2a** of the carbonyl group are shielded toward nucleophilic attack.[4,12] The enantiomers *ent*-**1a** and *ent*-**2a** are produced in the same way when enantiomeric amino alcohols are used.[7,13] Furthermore, the high tendency for crystallization of the *N*-sulfonyloxazolidines facilitates any upgrading and structure elucidation. Finally, the subsequent removal of the chiral auxiliary is easily accomplished by thiolysis[4,5,14] with 1,3-propanedithiol or via electrochemical detosylation.[15]

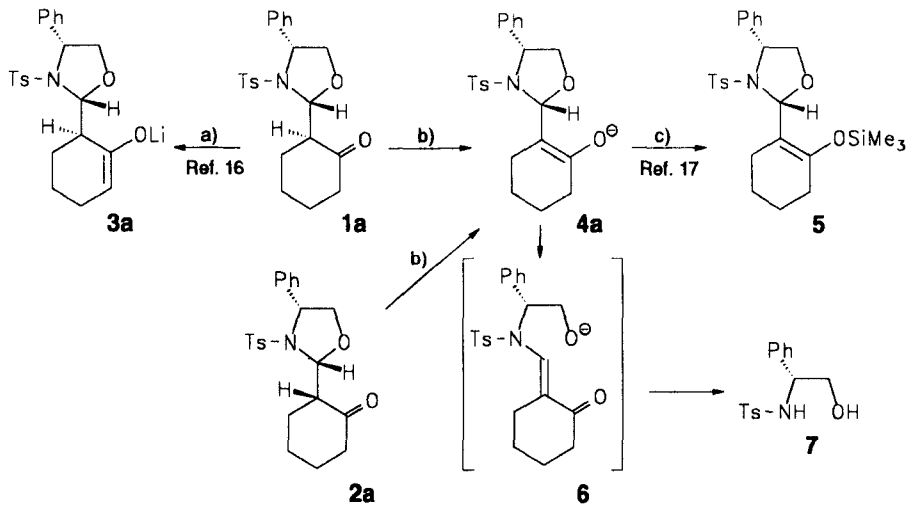


Scheme 1

The kinetically controlled deprotonation of the cyclohexanone **1a** and of its analogues with LDA furnishes the $\Delta^{1,6}$-enolate **3a** which undergoes highly diastereoselective aldol additions.[16] The thermodynamically favoured $\Delta^{1,2}$-enolate **4a** is passed during the synthesis of silyl enol ethers **5** by triethylamine-mediated trimethylsilylation,[17] however it turned out to be chemically highly unstable due to the potential leaving groups in ß-position leading after hydrolysis to the *N*-tosylamine **7** via the enamine **6**.

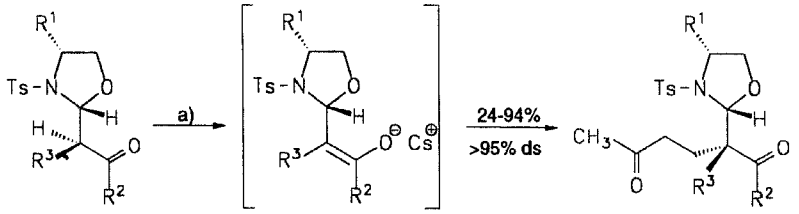
Both epimeric precursors **1** and **2** provide the same enolates of type **4**. These bear an exocyclic acetal-type stereocenter attached to an electron-rich double bond and we were interested to learn whether an effective face selection by approaching electrophiles would occur, as it is seen in the electronically reversed situation with enones[17] and 2-acyl derivatives.[12]

In order to find conditions for accomplishing efficient Michael reactions with cyclic ketones[7] **1a**, **1b**, and *ent*-**1c**,[13] numerous acceptors and bases were tested. In most cases, decomposition was detected. The



a) LDA, -78°C, THF. b) Base, r.t. c) TMSCl, LiI, NEt_3, THF.

Scheme 2



1 a-f 4 a-f 8 a-f

a) Cs_2CO_3 (15-45 mol%), 3-butene-2-one (1.2-10 eq), THF, r.t., 24-48 h.

1, 4, 8	R^1	R^2	R^3
a	C_6H_5	$(CH_2)_4$	
b	CH_2CH_3	$(CH_2)_4$	
c	C_6H_5	$(CH_2)_3$	
d	C_6H_5	C_6H_5	H
e[a]	CH_2CH_3	C_6H_5	H
ent-**f**[a]	$CH(CH_3)_2$	C_6H_5	H

a) Not isolated, directly converted into **14**.

Scheme 3

best results were obtained by using 3-butene-2-one (methyl vinyl ketone) and 10 - 15 mol-% of suspended cesium carbonate[18] in THF at room temperature. In all cases, a single diastereomer of the 1,5-diketone **8a**, **8b**, and *ent*-**8c**,[13] respectively, was isolated. Similarly, the 2-phenacyloxazolidine **1d** furnished the diastereomerically pure 1,5-diketone **8d**. Under the reaction conditions, the intermediate Michael adducts **8d**, **8e**, and *ent*-**8f**[13] undergo a rapid intramolecular aldolization.

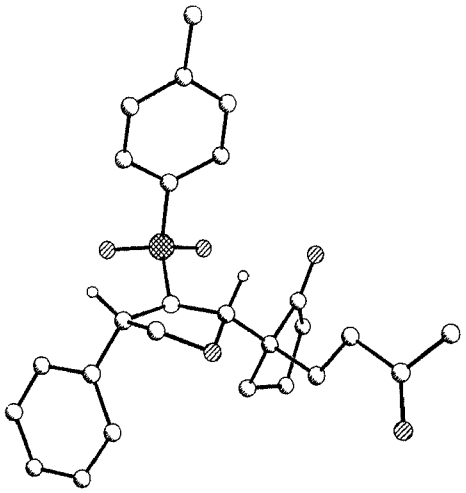
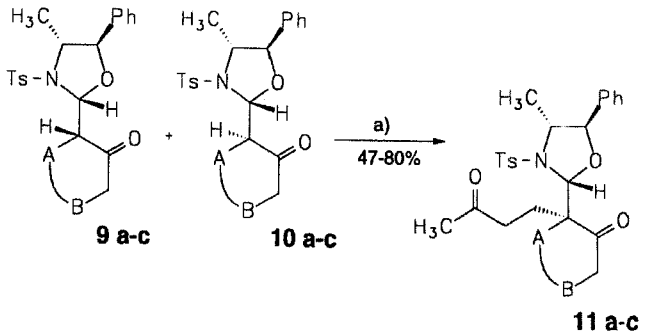


Figure 1. Molecular structure of compound *ent*-**8c** according to X-ray analysis.

The configurations of *ent*-**8c**[13,19,31] and of **8d**[20,31] (Figures 1 and 2) were elucidated by single-crystal X-ray analyses, and, as well though indirectly, of **8e** on a later step (**17e**, see below).

Similarly, starting from various epimeric mixtures (see Scheme 4) of norpseudoephedrine-derived cycloalkanones[10] **9a-c** and **10a-c** the diketones **11a-c** were prepared.



9 a-c 10 a-c 11 a-c

9, 10, 11	a	b	c
	A–B	-$(CH_2)_3$-	

a) Various mixtures of **9**, **10**:
9a, **10a** (100:0), Cs_2CO_3 (90mol-%), 3-butene-2-one (12 eq).
9b, **10b** (80:20), Cs_2CO_3 (50mol-%), 3-butene-2-one (12 eq).
9c, **10c** (20:80), Cs_2CO_3 (80mol-%), 3-butene-2-one (12 eq).

Scheme 4

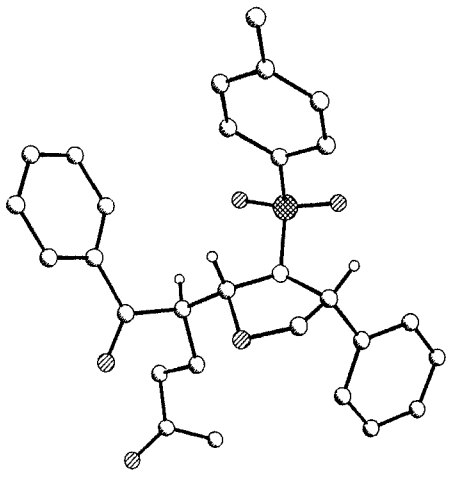


Figure 2. Molecular structure of compound **8d** according to X-ray analysis.

The high diastereoselectivity in the Michael addition of the enolates **4** to 3-buten-2-one, directed by the stereogenic center at C-2 of the oxazolidine ring, is surprising. The stereochemical result indicates that the enolate carbon atom is attacked from the *si*-face.

Table 1. Compounds **8**, **11**, **13**, **14**, **15**, **17**, **18** Prepared

Product	Educt	Yield (%)	$[\alpha]_D^{20}$ (c, CH_2Cl_2).	mp (°C) (solvent)[a]	Molecular Formula[b]	Selected IR Data (KBr) υ (cm^{-1})
8a	**1a**	65	-13.6 (1.6)	117 (E)	$C_{26}H_{31}NO_5S$ (469.6)	1715, 1690, 1345, 1165
8b	**1b**	24	+88.5 (1.0)	107 (E)	$C_{27}H_{31}NO_5S$ (421.6)	1700, 1345, 1160
ent-**8c**	*ent*-**1c**	45	+82.3 (0.4)	143 (EE/H)[c]	$C_{25}H_{29}NO_5S$ (455.6)	1730, 1705, 1355, 1140
8d	**1d**	65	-40.4 (2.0)	113 (E)	$C_{28}H_{29}NO_5S$ (491.6)	1700, 1675, 1350, 1165
11a	**9a, 10a**[d]	80	+15.5 (0.9)	[e]	$C_{27}H_{33}NO_5S$ (483.6)	1705, 1350, 1160
11b	**9b, 10b**[d]	47	+55.8 (1.0)	95 (E)	$C_{31}H_{33}NO_5S$ (531.7)	1710, 1350, 1165
11c	**9c, 10c**[d]	52	+67.1 (1.2)	155 (EE)	$C_{31}H_{33}NO_5S$ (531.7)	1700, 1660, 1350, 1160
13a	**8a**	30[f]	-56.6 (1.2)	173 (E)	$C_{26}H_{31}NO_5S$ (469.61)	3520, 1705, 1345, 1160
13b	**8a**	12[f]	-51.2 (1.1)	[g]	$C_{26}H_{31}NO_5S$ (469.6)	3450, 1700, 1350, 1165
14d	**1d**	22	-9.4 (1.3)	197 (E)	$C_{26}H_{31}NO_5S$ (469.6)	3390, 1705, 1355, 1165
14e	**1e**	94	+83.2 (1.0)	208 (E)	$C_{24}H_{29}NO_5S$ (443.5)	3510, 1700, 1345, 1160
ent-**14f**	*ent*-**1f**	84	-93.5 (1.0)	201 (E)	$C_{25}H_{31}NO_5S$ (457.6)	3510, 1705, 1335, 1155
15e	**14e**	91	-176.1 (1.1)	229 (E)	$C_{24}H_{27}NO_4S$ (425.5)	1670, 1610, 1345, 1165
ent-**15f**	*ent*-**14f**	86	+138.8 (1.3)	223 (EE)	$C_{25}H_{29}NO_4S$ (439.6)	1665, 1600, 1340, 1155
17a	**14e**	[h,i]	+74.7 (1.0)	139 (E)	$C_{24}H_{31}NO_5S$ (445.6)	3520, 3420, 1330, 1160
18a	**14e**	[h,i]	+103.1 (1.0)	160 (EE)	$C_{24}H_{31}NO_5S$ (445.6)	3540, 3500, 1335, 1160
17b	**14e**	87[j]	+81.6 (1.0)	181 (EE)	$C_{25}H_{33}NO_5S$ (459.6)	3500, 3460, 1345, 1165
17c	**14e**	85[j]	+62.4 (1.1)	146 (E)	$C_{26}H_{35}NO_5S$ (473.6)	3480, 1345, 1165
17d	**14e**	92[j]	+56.3 (1.1)	68 (E)	$C_{31}H_{37}NO_5S$ (535.7)	3460, 1335, 1155
17e	**14e**	55[j]	+66.0 (0.8)	126 (EE)	$C_{28}H_{37}NO_7S$ (531.7)	3450, 1750, 1340, 1165
ent-**17f**	*ent*-**14f**	84[j]	-75.3 (1.0)	174 (E)	$C_{26}H_{35}NO_5S$ (473.6)	3470, 1340, 1160
ent-**17g**	*ent*-**14f**	65[j]	-55.5 (1.0)	132 (E)	$C_{27}H_{37}NO_5S$ (487.6)	3460, 1345, 1155

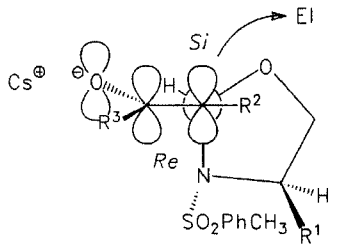
[a] E = diethyl ether, H = hexane.
[b] Satisfactory elemental analysis obtained (C±0.22%, H±0.24%).
[c] EE/H: EtOAc/hexane, 1:2.
[d] Various mixtures, see Scheme 4.
[e] Colourless oil.
[f] Combined yield 42%.
[g] Amorphous solid, mp not determined.
[h] With $Zn(BH_4)_2$: 63% **17a** and 37% **18a**; combined yield 100%.
[i] With *i*BuAlH: 51% **17a** and 39% **18a**; combined yield 90%.
[j] Traces of epimer **18b-g** could be detected in the crude product, see Scheme 7.

If accepting the hypothesis, that the parallel orientation of the enolate π -orbital and the adjacent electronegative *C-X*-bond contribute to the stabilization by π-σ* overlap and that the antiperiplanar approach of the electrophile is favoured,[21] both reactive conformations **4A** and **4B** could explain the observed stereochemical result (Figure 3). As clearly seen, conformation **4B** is at a disadvantage due to increased electrostatic repulsion between the enolate oxygen and the sulfonyl group and, as well, a severe allylic 1,3-strain.[22]

The enantiomerically pure 1,5-diketones **8** and **11** offer a wide scope of further synthetic applications. We disclose here examples which are based on intramolecular aldolization to complete a Robinson-type annulation.[23]

Prolonged stirring of **8a** (or of the mixture of starting ketones **1a** and methyl vinyl ketone), however, with cesium carbonate took a different path and led to the mixture of two epimeric bicyclo[3.3.1]nonan-9-

ones **13a** and **13b**, arising from the intermediate cyclohexanone enolate **12**.



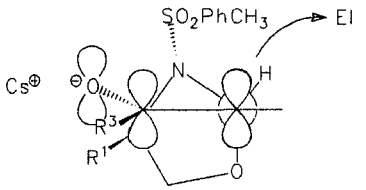
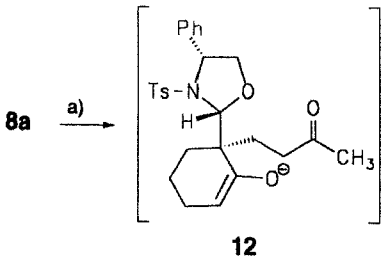
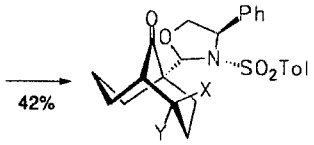


Figure 3





13a, b

	X	Y
13a	CH_3	OH
13b	OH	CH_3

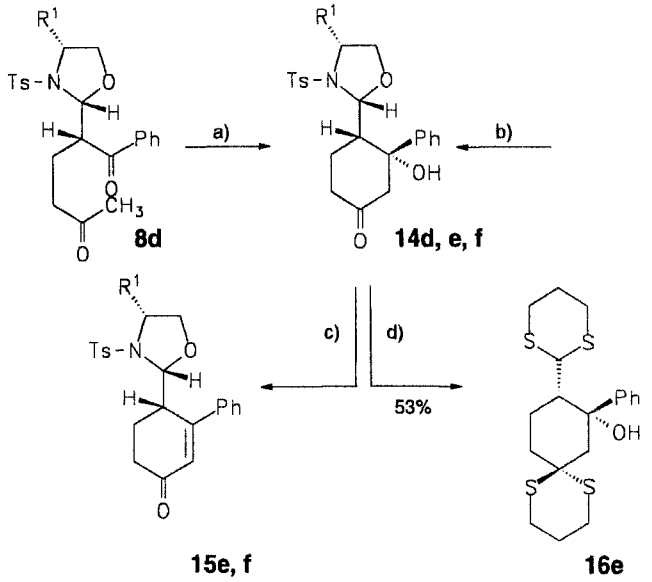
a) Cs_2CO_3,(15 mol-%), THF, r.t., 2d.

Scheme 5

The structure of these compounds was determined by comparison of the ^{13}C-NMR-data with those of fully elucidated analogues,[24] and by ^{1}H-^{1}H-NMR NOESY experiments.

Robinson annulation is accomplished by generating the kinetically favoured terminal enolate with sterically demanding bases.[25]

Diketone **8d** yielded on prolonged stirring with cesium carbonate in THF at r.t. the hydroxycyclohexanone **14d** as a single diastereomer. When the ketones **1d**, **e**, or *ent*-**1f**[13] and methyl vinyl ketone were treated with 15 mol% of cesium carbonate in the presence of 1 mol equivalent of 1,3-dimethyltetrahydro-2(1*H*)-pyrimidinone[26] (DMPU) in



a) Cs_2CO_3 (15 mol-%), THF, r.t., 1d. b) Cs_2CO_3 (15 mol%), DMPU (1 eq), 3-butene-2-one (1.5 eq), r.t., 2d, yields see Table 1.
c) $MeSO_3H$ (1.0 eq), molecular sieves 4Å, r.t., 1d, yield: **15e** (94%); *ent*-**15f** (84%). d) $MeSO_3H$ (0.2 eq), 1,3-propanedithiol (0.3 mL), r.t., 24 h, 53%.

Scheme 6

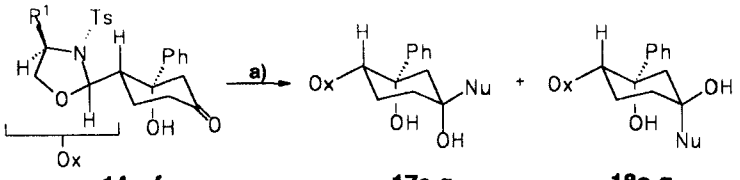
THF, the cyclohexanones **14d**, **e**, or *ent*-**14f**[13] resulted directly with high yield. No second diastereomer could be detected. Dehydration of **14e** or *ent*-**14f**[13] to furnish the cyclohexenones **15e** or *ent*-**15f**[13] was best accomplished by stirring the alcohols with catalytic amounts of methanesulfonic acid in the presence of molecular sieve 4 Å. The bis-dithiane **16e** was obtained from **14e** with 1,3-propanedithiol[4,5,14] under acid catalysis without the elimination of water.

The diastereotopic faces of the hydroxy ketone **14e** or *ent*-**14f**,[13] which are locked in a single chair conformation by both bulky equatorial substituents, are excellently differentiated by nucleophiles. Its reaction with L-Selectride®, methyllithium, Grignard reagents, or the cerium enolate[27] of ethyl acetate in THF furnished the bis-axial 1,3-diols **17** or *ent*-**17**,[13] repectively, with high diastereomeric excess.

The stereo-structure of the ester **17e** was determined by an X-ray crystal structure analysis.[28,31] It reveals two hydrogen bridges between both axial hydroxy groups and between one hydroxy group and the oxazolidine oxygen atom. The distinction between diaxial diols **17** and their axial-equatorial diastereomers **18** is already feasible on the ground of relative polarities and of ^{1}H-NMR spectroscopical data (in $CDCl_3$). Due to the intramolecular hydrogen bond diastereomeres **17**, in comparison to **18**, are less polar in TLC on silica gel and the ^{1}H-NMR absorption of the OH-group (in $CDCl_3$) is shifted by 2.6-3.1 ppm to lower field.[29]

Increasing portions of the diol **18a** are obtained by reduction of **14e** with diisobutylaluminium hydride (DIBALH)[30] or zinc borohydride. The conversion of both diols **17a** and **18a** into the dithianes **19a** and **20a**, respectively, proceeds without any difficulties.

In conclusion, Michael additions of chiral *N*-sulfonyloxazolidine-substituted ketones offer a powerful tool for the facile synthesis of stereochemically homogeneous cyclohexane derivatives. It should be realized that the pentasubstituted cyclohexanes **17** are assembled within only four synthetic steps from simple achiral starting materials (trialkyl orthoformate, acetophenone, methyl vinyl ketone and a nucleophilic



a) THF, -78°C, MNu, 1-4 h, aq. sat. NaCl, r.t.

	R^1	Nu	MNu	Solvent[a]	ds
17a/18a	C_2H_5	H	L-Selectride	100:0	> 95:5
			$Zn(BH_4)_2$	[b]	63:37
			DIBALH	[b]	57:43
17b/18b	C_2H_5	CH_3	MeMgCl	100:0	93:7
17c/18c	C_2H_5	C_2H_5	EtMgI	90:10	94:6
17d/18d	C_2H_5	$CH_2C_6H_5$	BnMgCl	80:20	94:6
17e	C_2H_5	$CH_2C(=O)OC_2H_5$	CH_2=C(OLi)OEt/ $CeCl_3$	100:0	> 95:5
ent-**17f**	$CH(CH_3)_2$	CH_3	MeMgCl	100:0	> 95:5
ent-**17g**	$CH(CH_3)_2$	C_2H_5	EtMgI	90:10	> 95:5

[a] Various mixtures of THF/Et_2O.
[b] Mixtures of THF/CH_2Cl_2 were used.

Scheme 7

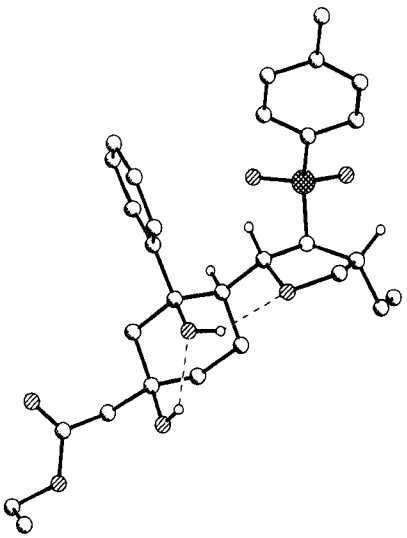
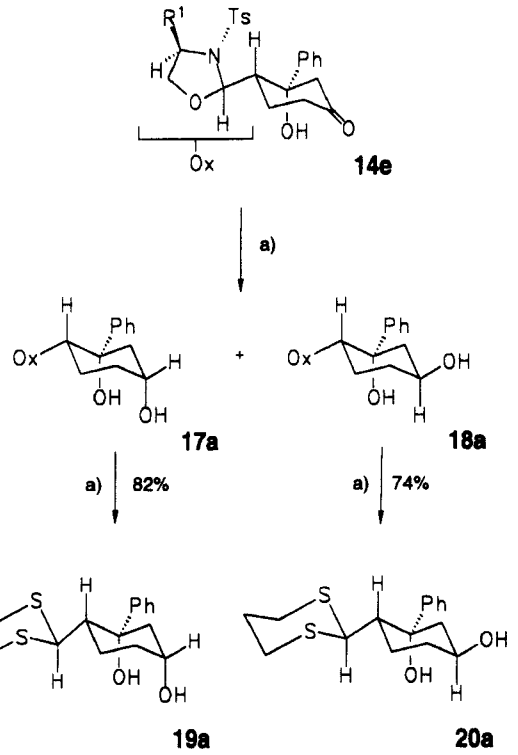


Figure 4. Molecular structure of compound **17e** according to X-ray analysis.

species R-M) under the stereodirecting influence of a chiral *N*-tosylamino alcohol. All steps are highly diastereoselective, and as a consequence, no diastereomer separation is required along the route.

Experiments involving metal-organic intermediates were carried out under Ar atmosphere with oven dried glassware . All solvents were purified by distillation and dried, if necessary, prior use. ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker AM 300 spectrometer. IR spectra were recorded on Perkin-Elmer 298 spectrophotometer. Optical rotations were recorded on Perkin-Elmer polarimeter 241. Melting points were obtained on a Mettler melting point apparatus FP 61 and



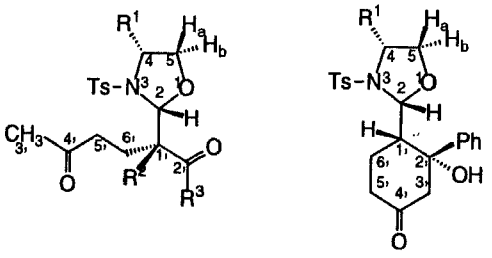
a) Reaction conditions see Scheme 7.
b) $MeSO_3H$ (0.2 eq), 1,3-propanedithiol (1.5 eq), CH_2CL_2, r.t., approx 24 h.

Scheme 8

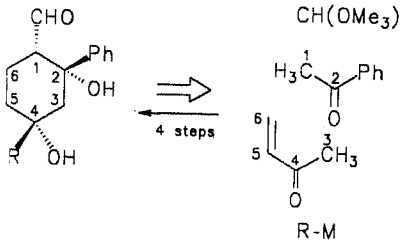
Table 2. Selected ^{1}H-NMR-Data of Oxazolidines **8**, **11**, **14**, **15**, **17**, and **18**[a, b]

Compound	2-H ($J_{2,1'}$)	1'-H	4-H ($J_{4,5a}$)	5-H_a ($J_{5a,5b}$)	5-H_b ($J_{4,5b}$)	2'-OH	4'-OH
8a	5.52 (s)	-	4.68 (dd, 6.8)	3.48 (dd, 9.1)	4.10 (dd, 2.0)	-	-
8b	5.34 (s)	-	3.57 (ddt, 5.8)	3.11 (ddd, 8.8)	3.63 (ddd, 1.5)	-	-
***ent*-8c**	5.05 (s)	-	4.77 (dd, 6.4)	3.48 (dd, 9.1)	4.07 (dd, 2.4)	-	-
8d	5.46 (d, 5.3)	4.11 (m)	4.81 (dd, 7.0)	3.75 (dd, 9.1)	4.16 (dd, 4.3)	-	-
11a	5.81 (s)	-	3.67 (dq, 6.4)	-	4.67 (d, 5.9)	-	-
11b	5.59 (s)	-	3.31 (dq, 6.4)	-	4.27 (d, 6.9)	-	-
11c	5.91 (s)	-	3.72 (dq, 6.4)	-	4.67 (d, 5.5)	-	-
14d	4.55 (d, 2.0)	3.29 (ddd)	4.49 (dd,6.5)	3.27 (dd, 9.2)	4.13 (dd, 3.1)	3.22 (d)	-
14e	4.38 (d, 2.0)	3.22 (ddd)	3.38 (ddt, 5.7)	2.75 (dd, 8.8)	3.59 (dd, 1.3)	3.21 (d)	-
***ent*-14f**	4.36 (d, 2.0)	3.23 (ddd)	3.10 (ddt, 5.6)	2.55 (dd, 9.0)	3.71 (d)	3.25 (m)	-
15e	4.68 (d, 2.5)	3.87 (m)	3.51 (ddt, 5.8)	2.82 (dd, 8.5)	3.56 (d)	-	-
***ent*-15f**	4.65 (d, 2.4)	3.87 (m)	3.24 (dd, 5.7)	2.65 (dd, 8.9)	3.87 (d)	-	-
17a	4.34 (d, 1.9)	2.81 (ddd)	3.39 (ddt, 5.6)	2.78 (ddd, 8.8)	3.61 (dd, 1.4)	3.78 (d)	4.51 (d)
18a	4.28 (d, 1.9)	2.70 (ddd)	3.38 (ddt, 5.8)	2.75 (ddd, 8.9)	3.58 (dd, 1.3)	3.23 (m)	1.89 (m)
17b	4.35 (d, 1.9)	2,76 (m)	3.39 (ddd, 5.6)	2.78 (dd, 8.7)	3.61 (dd, 1.5)	3.82 (d)	4.96 (s)
17c	4.35 (d, 1.9)	2.76 (ddd)	3.39 (ddt, 5.7)	2.78 (ddd, 5.7)	3.61 (dd, 1.6)	3.84 (s)	4.83 (s)
17d	4.30 (d, 1.9)	2.68 (ddd)	3.37 (ddt, 6.2)	2.75 (m)	3.58 (dd, 1.4)	3.86 (s)	4.92 (s)
17e	4.33 (d, 1.5)	2.75 (m)	3.38 (dd, 6.2)	2.77 (dd, 9.0)	[c]	3.60 (d)	5.08 (s)
***ent*-17f**	4.33 (d, 1.8)	2.78 (m)	3.10 (dd, 5.9)	2.54 (dd, 9.0)	3.71 (d)	3.8-4.1[d]	
***ent*-17g**	4.32 (d, 1.9)	2.75 (ddd)	3.10 (dd, 5.6)	2.56 (dd, 8.9)	3.72 (d)	[d]	[d]

[a] 300 MHz, $CDCl_3$
[b] The numbering used in Table 2 does not follow the IUPAC nomenclature.



[c] not clearly detectable, broad multiplett.
[d] broad multiplett.



Scheme 9

are uncorrected. Products were purified by flash column chromatography on silica gel (60-200 mesh) and/or by recrystallization. Ketones **1e** and ***ent*-1f** were prepared according to ref. 8. **1e**, yield 63%, R_F = 0.39 (EtOAc/cyclohexane, 1:2), $[\alpha]_D^{20}$ = +67.9 (c = 1.1, CH_2Cl_2), mp 182 °C (Et_2O), $C_{20}H_{23}NO_4S$ (373.5). ***ent*-1f**, yield 65%, R_F = 0.42 (EtOAc/cyclohexane, 1:2), $[\alpha]_D^{20}$ = -174.1 (c = 1.1, CH_2Cl_2), mp 135 °C (Et_2O), $C_{21}H_{25}NO_4S$ (387.5).

Table 3. Selected ^{13}C-NMR-Data of Oxazolidines **8**, **11**, **14**, **15**, **17**, and **18**[a, b]

Compound	C-2	C-1'	C-2'	C-4'
8a	93.40	53.66	210.83	208.01
8b	92.63	53.42	210.72	208.10
ent-**8c**	93.80	54.38	218.81	207.87
8d	92.64	49.59	199.65	207.81
11a	92.8	55.3	210.5	207.9
11b	99.4	61.8	211.9	207.4
11c	94.0	51.7	197.6	208.1
14d	91.93	47.56	78.86	208.19
14e	91.26	47.04	78.65	208.28
ent-**14f**	91.42	46.94	78.69	208.26
15e	93.06	39.96	158.50	199.65
ent-**15f**	93.43	40.12	158.76	199.69
17a	91.76	47.88	77.88	66.86
18a	91.56	47.75	77.00	67.33
17b	91.68	47.65	77.93	69.68
17c	91.73	47.99	77.86	71.54
17d	91.62	47.90	77.88	71.96
17e	91.55	47.82	78.60	77.32
ent-**17f**	91.89	47.61	77.98	69.65
ent-**17g**	91.96	47.95	77.95	71.52

a) 75 MHz, $CDCl_3$

b) The numbering used in Table 3 does not follow the IUPAC nomenclature. For numbering see Table 2.

Diketones 6 and 10 via Michael Addition; General Procedure:

To a suspension of **1**, **2** or mixtures thereof (1.0 mmol) and cesium carbonate (49 mg, 0.15 mmol) in THF (10 mL) DMPU (120 µL, 1 mmol) and freshly distilled 3-butene-2-one (0.10 mL, 1.2 mmol) are added and the reaction mixture is stirred at r.t. until complete conversion of **1** or **2** is detected by TLC (approx. 24 h). 2N HCl (0.5 mL) and sat. aq. NaCl (5 mL) are added and the mixture is stirred for additional 5 min. The aq. solution is extracted with EtOAc (3 x 10 mL), the organic layers are washed with sat. aq. $NaHCO_3$ (2 mL) and dried (Na_2SO_4). After removal of the solvent at reduced pressure the residue is purified via flash column chromatography on silica gel with EtOAc/cyclohexane (1:8-1:2) and recrystallized from Et_2O/CH_2Cl_2. Yields see Table 1.

The compounds **11** were prepared by reaction of various mixtures of **9** and **10** (see Scheme 4) with cesium carbonate and 12 eq. of 3-buten-2-one.

Condensation of 1a and 3-Butene-2-one under Forced Conditions; [1*R*,1(2*R*,4*R*),4*S*,5*S*]- and [1*R*,1(2*R*,4*R*),4*R*,5*S*]-4-Hydroxy-4-methyl-1-{[3-(4-toluenesulfonyl)-4-phenyl-1,3-oxazolidin-2-yl]}-bicyclo[3.3.1]nonan-9-one (13a and 13b):

1a (2.00 g, 5.0 mmol), cesium carbonate (1.63 g, 5 mmol) and freshly distilled 3-buten-2-one (0.83 mL, 10 mmol) were stirred as described above for 3 d. Chromatographic separation of the crude product on silica gel (60g) with ether/pentane 6:1 as eluent afforted **8a** (532 mg, 22%, R_F = 0.27 (Et_2O/pentane, 2:1)), **13a** (265 mg, 11%) and **13b** (285 mg, 12%).

13a, R_F = 0.14 (Et_2O), $[\alpha]_D^{20}$= -56.6 (*c*=1.2, CH_2Cl_2), mp 173 °C (Et_2O), IR (KBr): 3520 (OH), 1705 cm^{-1} (C=O).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.93 (ddd, 2-H_{eq}); 1.22 (s, 3H, 4-CH_3); 1.43 (ddd, 3-H_{ax}); 1.63 (m, 6-H); 1.65 (m, OH); 1.77 (ddd, 2-H_{ax}); 1.93-2.05 (m, 4H, 3-H_{eq}, 6-H, 7-H); 2.23-2.30 (m, 3H, 5-H, 8-H); 2.46 (s, 3H, tosyl-CH_3); 3.43 (dd, 5'-H_a); 4.27 (dd, 5'-H_b); 4.95 (dd, 4'-H); 5.77 (s, 2'-H); 7.27-7.83 (m, 9H, aromatic).

$J_{2eq,3ax}$ = 1.2 Hz, $J_{2eq,3eq}$ = 6.7 Hz, $J_{2ax,2eq}$ = 13.4 Hz, $J_{2ax,3eq}$ = 7.0 Hz, $J_{2ax,3ax}$ = 13.1Hz, $J_{4',5'a}$ = 7.4 Hz, $J_{4',5'b}$ = 3.1 Hz, $J_{5'a,5'b}$ = 9.0 Hz.

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 19.69 (C-7), 21.59 (tosyl-CH_3), 27.10 (C-2), 28.18 (C-4-CH_3), 30.53 (C-6), 34.32 (C-3), 38.12 (C-8), 53.31 (C-1), 59.64 (C-5), 61.64 (C-4'), 69.67 (C-5'), 73.84 (C-4), 94.82 (C-2'), 126.72, 127.56, 128.42, 128.53, 130.15, 133.96, 138.78, 144.64 (12 C, aromatic), 216.74 (C-9).

13b, R_F=0.19 (Et_2O), $[\alpha]_D^{20}$= -51.3 (*c*=1.1, CH_2Cl_2), IR (KBr): 3450 (OH), 1700 cm^{-1} (C=O).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.97 (ddd, 2-H_{eq}); 1.04 (s, 3H, 4-CH_3); 1.22-1.47 (m, 2H); 1.52-1.72 (m, 1H); 1.80-2.15 (m, 2H); 2.22-2.48 (m, 5H,); 2.46 (s, 3H, tosyl-CH_3); 3.43 (dd, 5'-H_a); 4.24 (dd, 5'-H_b); 4.98 (dd, 4'-H); 5.76 (s, 2'-H); 7.29-7.83 (m, 9H, aromatic).

$J_{2eq,3ax}$ = 1.7 Hz, $J_{2eq,3eq}$ = 7.1 Hz, $J_{2ax,2eq}$ = 13.9 Hz, $J_{4',5'a}$ = 7.3 Hz, $J_{4',5'b}$ = 2.9 Hz, $J_{5'a,5'b}$ = 9.0 Hz.

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 20.01 (C-7), 21.59 (tosyl-CH_3), 25.94 (C-2), 29.05 (C-4-CH_3), 29.51 (C-6), 35.29 (C-3), 38.78 (C-8), 53.24 (C-1), 59.71 (C-5), 61.63 (C-4'), 69.63 (C-5'), 73.94 (C-4), 94.64 (C-2'), 126.52, 127.60, 128.42, 130.09, 133.83, 138.57, 144.65 (12 C, aromatic), 216.21 (C-9).

Robinson Annulation of Ketone 1e; [3*R*,4*S*,4(2*R*,4*R*)]-4-[4-Ethyl-3-(4-toluenesulfonyl)-1,3-oxazolidin-2-yl]-3-hydroxy-3-phenylcyclohexanone (14e); Typical Procedure:

1e (1.87 g, 5 mmol), cesium carbonate (0.24 g, 0.75 mmol) were suspended in THF (20 mL); DMPU (0.60 mL, 5 mmol) and freshly distilled 3-butene-2-one (0.45 mL, 5 mmol) were added sucessively. After 48 h stirring at r.t. the reaction was quenched by addition of 2N HCl (2 mL) and sat. aq. NaCl (5 mL). Stirring was continued for 5 min, the aq. layer was extracted with EtOAc and CH_2Cl_2 (approx. 2 x 15 mL, each) until the solution became clear. The combined org. layers were washed with sat. aq. $NaHCO_3$ (5 mL) and dried (Na_2SO_4). After partial evaporation of the solvent at reduced pressure the product started its crystallization. Et_2O (5 mL) was added and **14e** (0.75 g, 34%, R_F = 0.21 (EtOAc/cyclohexane, 1:2)) was isolated as colorless cubes. The residue was purified via flash column chromatography on silica gel (70 g) with EtOAc/cyclohexane (1:4) and yielded additional **14e** (1.31 g, 59%). Combined yield 94%.

Dehydration of Aldols 14e and *ent*-14f; [4*S*,4(2*R*,4*R*)]-4-[4-Ethyl-3-(4-toluenesulfonyl)1,3-oxazolidin-2-yl]-3-phenylcyclohex-2-enone 14e and [4*R*,4(2*S*,4*S*)]-4-[4-Isopropyl-3-(4-toluenesulfonyl)1,3-oxazolidin-2-yl]-3-phenylcyclohex-2-enone *ent*-15f:

To a mixture of **14** (1.0 mmol) and molecular sieve (4Å, 5 g) in CH_2Cl_2 (5 mL) $MeSO_3H$ (0.1 mL) was added and the reaction mixture was stirred overnight. Solid K_2CO_3 (500 mg) was added and the stirring was continued for 15 min; then the mixture was poured onto silica gel and eluated with CH_2Cl_2 (4 x 15 mL). The solvent was evaporated and the product was crystallized from Et_2O, the residue was purified by flash column chromatography with EtOAc/cyclohexane (1:5). Yields see Table 1.

General Procedure for Preparation of Diols 17, 18:

To a solution of **14** (1.0 mmol) in THF (5 mL) stirring at -78 °C a solution of MNu (amount and solvent see Scheme 7) is added dropwise. The reaction mixture is stirred for 1 to 4 h to complete conversion of **14**. The reaction is quenched by addition of sat. aq. NH_4Cl (0.2 mL), the mixture is allowed to warm up to r.t. and sat. aq. NaCl (5 mL) is added. The aqueous layer is washed with EtOAc (3 x10 mL) and the combined organic layers are dried (Na_2SO_4). After evaporation of the solvent at reduced pressure the residue is purified by flash column chromatography on silica gel with EtOAc/cyclohexane (various mixtures).

Conversion into Dithianes;

Thiolysis of 17a and 18a; (1*R*,3*R*,4*S*)- and (1*S*,3*R*,4*S*)-4-(1,3-Dithian-2-yl)-3-phenyl-1,3-cyclohexanediol 19a and 20a:

To a solution of **17a** or **18a** (446 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) 1,3-propanedithiol (0.15 mL, 1.5 mmol) and $MeSO_3H$ (approx. 0.05 mL) were added and the reaction mixture was stirred at r.t. for 24 h. After completion of the reaction monitored by TLC, solid K_2CO_3 (250 mg) was added and the suspension was allowed stirring additional 5 min. The insoluble material was filtered off and the evaporation and purification by flash chromatography on silica gel (21 g) with Et_2O/pentane (1:8) afforded the dithiane.

19a, R_F = 0.33 (EtOAc/cyclohexane, 1:2), $[\alpha]_D^{20}$ = +27.5 (*c* = 1.0, CH_2Cl_2), mp 141 °C (EtOAc), IR (KBr):3410 (OH), 2880, 2860 (CH), 1575 (C=C), 900 (C-S), 755 u. 695cm^{-1} (monosubst. phenyl), $C_{16}H_{22}O_2S_2$ (310.5).

300 MHz-^{1}H-NMR: δ = 1.56-2.30 (m, 2H, dithianyl, 7H, cyclohexyl); 2.43-2.77 (m, 4H, -S-CH_2-R); 3.84 (d, 2'-H); 3.87-3.99 (m, 2H, 1-H, 1-OH), 4.29 (m, 3-OH), 7.21-7.42 (m, 5H, phenyl).

$J_{4,2'}$ = 1.2 Hz.

75 MHz-^{13}C-NMR: δ = 18.13 (C-5), 25.56 (C-5'), 30.83 (C-4'), 31.69 (C-6'), 33.19 (C-6), 45.41 (C-2), 50.16 (C-4), 50.70 (C-2'), 66.80 (C-1), 79.95 (C-3), 124.26, 126.99, 128.52, 146.10 (6C, phenyl).

20a, R_F = 0.15 (EtOAc/cyclohexane, 1:2), $[\alpha]_D^{20}$ = +43.4 (*c* = 0.9, CH_2Cl_2), mp 51 °C (colorless foam), IR (KBr): 3420 (OH), 1585 (C=C) and 1050 cm^{-1} (C-S), $C_{16}H_{22}O_2S_2$ (310.5).

300 MHz-^{1}H-NMR: δ = 1.33-1.82 (m, 3H, cyclohexyl); 1.88 (m, 1-OH); 1.92-2.23 (m, 2H, dithianyl, 4H, cyclohexyl); 2.54-2.82 (m, 4H, -S-C*H*$_2$-R); 3.28 (d, 3-OH); 3.87 (d, 2'-H); 4.12 (m, 1-H); 7.26-7.51 (m, 5H, phenyl).

$J_{4,2'}$ = 1.7 Hz.

75 MHz-^{13}C-NMR: δ = 22.10 (C-5), 25.61 (C-5'), 30.91 (C-4'), 31.78 (C-6'), 35.11 (C-6), 49.91 (C-2), 50.01 (C-4), 50.36 (C-2'), 67.00 (C-1), 79.23 (C-3), 124.28, 126.94, 128.56, 146.48 (6C, phenyl).

Thiolysis of 14e; (8*R*,9*S*)-8-Hydroxy-8-phenyl-9-(1,3-dithian-2-yl)-1,5-dithiaspiro[5.5]undecane 15e:

To a solution of **13e** (444 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) 1,3-propanedithiol (0.30 mL, 3 mmol) and $MeSO_3H$ (0.1 mL) were added and the reaction mixture was stirred at r.t. for 24 h. After completion of the reaction monitored by TLC, solid K_2CO_3 (350 mg) was added and the suspension was allowed stirring for additional 5 min. The crude reaction mixture was poured onto silica gel and eluated with CH_2Cl_2 (4 x 15 mL). After the evaporation and purification by flash chromatography on silica gel (35 g) with EtOAc/cyclohexane (1:5) the dithiane **15e** (211 mg, 53%) was isolated.

15e, R_F = 0.45 (EtOAc/cyclohexane, 1:2), $[\alpha]_D^{20}$ = -35.9 (*c* = 0.92, CH_2Cl_2), mp 179 °C (EtOAc/cyclohexane, 1:2), IR (KBr): 3330 (OH), 2870 (CH), 1570 (C=C), 900 cm^{-1} (C-S), $C_{19}H_{26}OS_4$ (398.6).

300 MHz-^{1}H-NMR: δ = 1.72-2.48 (m, 4H, dithianyl, 7H, cyclohexyl); 2.62-3.00 (m, 8H, dithianyl, -S-C*H*$_2$-R); 3.96 (d, 2'-H); 4.79 (s, 8-OH); 7.2-7.61 (m, 5H, phenyl).

$J_{2,1'}$ = 1.7 Hz.

75 MHz-^{13}C-NMR: δ = 20.13, 25.09, 25.69, 26.20 (4C, R-CH_2-R), 30.48, 31.52, 38.64 (4C, S-CH_2-R), 48.27 (C-6), 48.76 (C-9), 49.58 (C-7), 50.80 (C-2'), 77.43 (C-8), 124.99, 126.85, 128.22, 145.52 (6C, aromatic).

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(19) Crystal size 0.3∗0.3∗0.6mm^3, space group $P2_12_12_1$, a = 1188.5 (1)pm, b = 1375.6 (1)pm, c = 1429.5 (1)pm, V = 2.34nm^3, Z = 4, μ(CuKα) = 1.486mm^{-1}, 3014 intensities were collected with 2° ≤ 2Θ ≤ 120° at 293K and 2810 symmetry independent reflections with F > 3σ(F) remained for structure solution and refinement on F.
The structure was solved with the Patterson method and refined to R = 0.037 (wR = 0.048), H atoms located by difference electron-density synthesis and refined with fixed individual displacement parameters using a "riding" model, all other atoms refined anisotropically.

(20) Crystal size 0.1∗0.3∗0.5mm^3, space group $P2_1$, a = 875.4 (1)pm, b = 1680.6 (1)pm, c = 878.6 (1)pm, β = 102.68 (1)°, V = 1.261nm^3, Z = 2, μ(CuKα) = 1.459mm^{-1},7361 intensities were collected with 10° ≤ 2Θ ≤ 120° at 293K and 3723 symmetry independent reflections remained for structure solution and refinement on F^2.
The structure was solved with the Patterson method and refined to wR(F^2)= 0.0965, H atoms located by difference electron-density synthesis and refined with fixed individual displacement parameters using a "riding" model, all other atoms refined anisotropically.

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