Enantioselective Preparation of 2-Aminomethyl Carboxylic Acid Derivatives: Solving the β^2-Amino Acid Problem with the Chiral Auxiliary 4-Isopropyl-5,5-diphenyloxazolidin-2-one (DIOZ)

Preliminary Communication

by **Dieter Seebach***, **Laurent Schaeffer**[1]), **François Gessier**[1]), **Pascal Bindschädler**[2]), **Corinna Jäger**[3]), **Delphine Josien**[1]), **Sascha Kopp**[2]), **Gérald Lelais**[4]), **Yogesh R. Mahajan**[4]), **Peter Micuch**[1]), **Radovan Sebesta**[1]), and **Bernd W. Schweizer**

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, Hönggerberg-HCI, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich

Multigram amounts of suitably protected β^2-amino acids with 17 of the 20 proteinogenic side chains are prepared by diastereoselective reactions of Li, B, or Ti enolates of the corresponding 3-acyl-4-isopropyl-5,5-diphenyloxazolidin-2-ones (acyl-DIOZ; **1**) with appropriate electrophiles (amidomethylation, hydroxyalkylation, (benzyloxycarbonyl)methylation) in yields of 55–90% and with diastereoselectivities of 80 to >97% (*Scheme*). The primary products **2**–**8** thus obtained are converted to protected β^2-amino acids by standard procedures (*Table 1*). Many of the DIOZ derivatives are highly crystalline compounds (31 X-ray crystal structures in *Table 2*). The chiral auxiliary DIOZ, readily prepared in either enantiomeric form, is recovered with high yield.

β-Peptides, which consist of homologs of α-amino acids, have turned out to present a new world of peptide chemistry. While the functional groups in the chain (the amide bonds) and in the side chains (of Arg, Asp, Glu, His, Lys, Met, Ser, Thr, Trp, and Tyr) are identical, there is *just* an additional backbone CH_2 group in each amino acid moiety. Even this causes dramatic effects: secondary structures differ fundamentally (in number, shape, size, and polarity) and are more stable and predictable at short chain length [1][2]; there is total enzymatic stability (against peptidases and proteases) [3], metabolic stability in rats has been demonstrated [4], even microbial degradation is slow [5]. On the other hand, the activities of an α-peptidic hormone and of an α-peptidic amphipathic helix can be mimicked by β-peptides [6], and strong binding of certain β-peptides to DNA of mammalian cells has been detected [7].

There are two ways of inserting CH_2 groups into the backbone of peptides: between the C=O group and the α-C-atom ($\rightarrow \beta^3$-amino acid) or between the α-C-atom and the N-atom ($\rightarrow \beta^2$-amino acid), and it turns out that the latter change has the more intriguing effects, leading to turn structures [2] or to a novel type of helix, which consists of alternating ten- and twelve-membered H-bonded rings [1][8].

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[3]) Part of Advanced Laboratory Course, ETH-Zürich, 2002/2003.

[4]) Part of the projected Ph.D. Theses of *G. L.* and of *Y. R. M.*, ETH-Zürich, 2003.

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While the 20 β^3-amino acids with proteinogenic side chains are readily available[5]) for solid-phase synthesis by the Fmoc strategy [9], the β^2-analogs are not. There are many recent papers – some with bombastically general titles – announcing more or less ingenious preparations of β^2-amino acids, and when one looks at the details there are only the trivial Me, i-Pr, or Bn side chains[6]).

For our ongoing work on the synthesis of more-complex β^2/β^3- and all-β^2-peptides, we needed to have ample access to all 20 – properly protected – β^2-amino acids with the proteinogenic side chains. Thus, *ca.* 5-g amounts of each were prepared from the *N*-acyl-oxazolidin-2-ones **1a**–**1p**[7]) (*Evans* methodology; *Scheme*). Most important was the *Mannich* reaction of the Ti-enolates with $MeOCH_2NHZ$ [11][12] (**1a**–**1j** → **2a**–**2j**) and their aldol addition with trioxane (→ **5**, **6**). B-Enolates served for aldol addition to acetaldehyde and to formyl-indol (→ **3**, **4**), and Li-enolates were used for the reaction with ICH_2CO_2Bn (→ **7**, **8**). In *Table 1*, the conversions of the primary products **2**–**8** to *C*-, *N*-, and/or side-chain protected β^2-amino acids are outlined, together with the overall yields and leading references to the methods used. Since both enantiomers of our modified *Evans* auxiliary [12][8]) DIOZ are available, the enantiomers of the compounds described here are equally well accessible.

One of the advantages of DIOZ is that most of its derivatives are crystalline [13], so that we could make use of X-ray crystal-structure analyses for safe configurational assignments (*Table 2*). Another advantage is the insolubility of the auxiliary itself, which is readily recovered (*ca.* 90%) by filtration after cleavage from the products.

All products, the formulae of which are shown in the *Scheme* and in *Table 1*, as well as most of the intermediates (*cf.* **9**–**15** in *Table 2*) formed on the way from the primary products **1**–**8** to the amino acids (see *Table 1*) have been fully characterized (IR, NMR, $[\alpha]_D$, MS, elemental analyses). This is also true of other DIOZ derivatives **16**–**32** (*Table 2*) prepared in the course of our search for alternative general routes to β-amino acids[9]).

From the β^2-amino acids listed in *Table 1*, we are in the process of preparing β^2-dipeptides or β^2/β^3-dipeptides for solid-state fragment coupling [9d]. As in α-peptide and protein chemistry, the β-amino acids with the functional groups CO_2H, NH_3, guanidyl, imidazolyl, OH, SH, $CONH_2$ in the side chain are especially important for salt-bridge formation, derivatization (*cf.* phosphorylation, glycosylation *etc.*), metal complexation (*cf.* zinc fingers), disulfide-bridge formation, and strong H-bonding, effects that we are presently probing in the world of β-peptides.

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5) We synthesized only Fmoc-β^3hCys(Trt)-OH and Fmoc-β^3hHis(Trt)-OH. The other 18 Fmoc-β^3hXaa(PG)-OH are commercially available (PG = acid-labile protecting group).

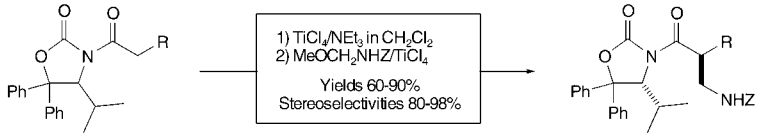
6) For a recent review article on β-amino acid syntheses, see [10].

7) Most acid derivatives for the preparation of **1a**–**1p** are commercially available; two were prepared by reductive deamination of the corresponding amino acids (Ile, Met).

8) Generous supply of DIOZ by the Kilolab of *Novartis Pharma AG* (Drs. *Thomas Leutert* and *Luigi La Vecchia*, Basel) is gratefully acknowledged. An *Organic Syntheses* procedure has been checked by the editors and will appear in the next issue of the series; a copy of the procedure can be requested from the corresponding author *D. S.*

9) Details about the results of these investigations will be described elsewhere.

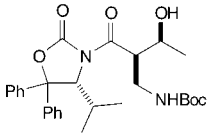
Scheme. *Starting Materials* N-*Acyloxazolidinones* **1a**–**1p** *and Products* **2**–**8** *from the Reaction of* N-*Acyloxazolidinone Enolates with Electrophiles.* For abbreviations, see caption of *Table 1*; y = yield, ds = diastereoselectivity.



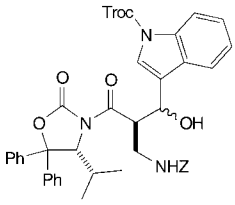
(*R*)- or (*S*)-**1a–1p** → **2a–2j** from (*R*)-**1a–1j**

	a	b	c	d	e	f	g	h	i
R	Me	Me_2CH	Me_2CHCH_2	$Br(CH_2)_2$	$Br(CH_2)_3$	$Br(CH_2)_4$	$PhCH_2$	$TBDPSOC_6H_4CH_2$	(*S*)-EtCH(Me)

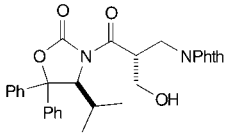
	j	k	l	m	n	o	p
R	$MeS(CH_2)_2$	$BocNHCH_2$	$ZNHCH_2$	$PhthNCH_2$	(1-trityl-1*H*-imidazol-4-yl)CH_2	$BocOCH_2$	$BocOCH_2CH_2$



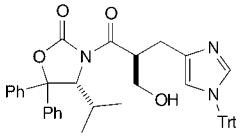
3 from (*R*)-**1k**, Bu_2BOTf/NEt_3, MeCHO, 91% y, 97% ds



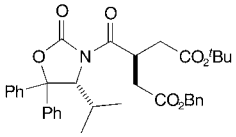
4 from (*R*)-**1l**, Bu_2BOTf/NEt_3, 1-Troc-3-formyl-1*H*-indol, 52% y



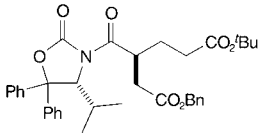
5 from (*S*)-**1m**, $TiCl_4/NEt_3$, trioxane, 85% y, 97% ds



6 from (*R*)-**1n**, $TiCl_4/NEt_3$, trioxane, 72% y, 90% ds



7 from (*R*)-**1o**, LHMDS, ICH_2CO_2Bn, 71% y, >97% ds



8 from (*R*)-**1p**, LHMDS, ICH_2CO_2Bn, 55% y, >97% ds

Table 1. *Seventeen of the Twenty β^2-Amino Acid Derivatives with Proteinogenic Side Chains Prepared from the Primary Products* **2**–**8**. All products have (*S*)-configuration, except for the (*R*)-β^2hSer and (*R*)-β^2hThr derivatives. For the general methodology, see [11–13] and refs. cit. therein. For previous papers by our group on the preparation of β^2-amino acids, see [1c][2][9d][12][14][6]). The preparation of the two missing Asn and Gln derivatives is underway in our laboratory; β^2-amino acid number 20: β^2hGly≡β^3hGly. The abbreviations Boc, Fmoc, Z, Troc, DBU, TFA, Trt are common in peptide chemistry. ADDP = 1,1′-(azodicarbonyl)dipiperidine, DIAD = diisopropyl azodicarboxylate, DMAP = 4-(dimethylamino)pyridine, DPPA = diphenylphosphoryl azide, GR = guanidylation reagent = 1,2-bis[(*tert*-butoxy)carbonyl-1*H*-pyrazole-1-carboxamidine, LHMDS = lithium hexamethyldisilazide, Phth = phthaloyl, Su = succinimidyl, TBAF = tetrabutylammonium fluoride, TBDPS = (*tert*-butyl)diphenylsilyl, Tf = trifluoromethanesulfonyl, TMSE = 2-(trimethylsilyl)ethyl.

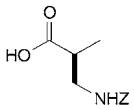
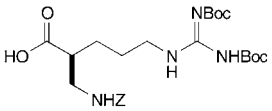
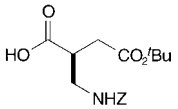
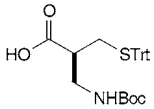
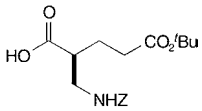
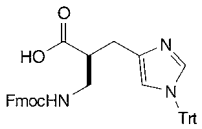
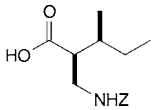
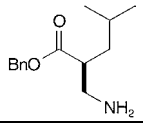
β^2-Amino Acid Derivative		Precursor	Step(s)	Overall yield [%]	References
Z-β^2hAla-OH		**2a**	LiOH/THF/H_2O	91	
Z-β^2hArg(Boc)$_2$-OH		**2e**	1. NaN_3/DMF 2. PPh_3/GR/THF/H_3O 3. LiOH/THF/H_2O_2	56	[15]
Z-β^2hAsp(^{t}Bu)-OH		**7**	1. H_2/Pd-C/THF 2. DPPA/NEt_3/PhMe 3. BnOH/PhMe 4. LiOH/THF/H_2O_2	32	[16]
Boc-β^2hCys(Trt)-OH		**5**	1. PBu_3/ADDP/TrtSH/THF 2. TMSEOLi/THF 3. $(NH_2CH_2)_2$/BuOH/THF 4. Boc_2O/MeOH/dioxane 5. TBAF/THF	25	[17][18]
Z-β^2hGlu(^{t}Bu)-OH		**8**	1. H_2/Pd-C/THF 2. DPPA/NEt_3/PhMe 3. BnOH/PhMe 4. LiOH/THF/H_2O_2	13	[16]
Fmoc-β^2hHis(Trt)-OH		**6**	1. BnOLi/THF 2. DIAD/PPh_3/HN_3/THF 3. H_2/Pd-C/EtOH 4. FmocOSu/Na_2CO_3/H_2O	24	[19]
Z-β^2hIle-OH		**2i**	LiOH/THF/H_2O	66	
H-β^2hLeu-OBn		**2c**	1. BnOLi/THF 2. H_2/Pd-C/MeOH 3. TsOH/BnOH/benzene	83	

Table 1 (cont.)

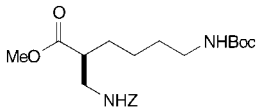
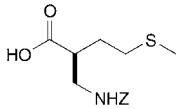
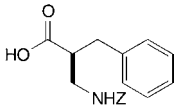
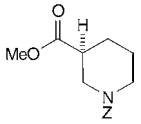
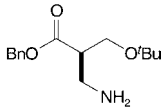
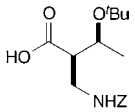
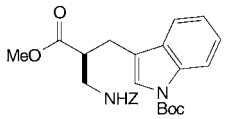
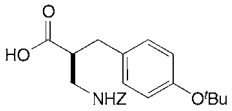
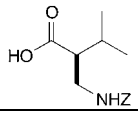
Z-β^2hLys(Boc)-OMe		**2f**	1. NaN_3/DMF 2. Boc_2O/*Lindlar* cat./MeOH 3. LiBr/DBU/MeOH	80	[20]
Z-β^2hMet-OH		**2d**, **2j**	NaOH/THF/MeOH	80	
Z-β^2hPhe-OH		**2g**	NaOH/THF/MeOH	91	
Z-β^2h-Pro-OMe		**2e**	1. NaH/Bu_4NI/DMF 2. LiBr/DBU/MeOH	48	
H-β^2hSer(^{t}Bu)-OBn		**5**	1. Isobutylene/CH_2Cl_2/H_2SO_4 2. BnOLi/THF 3. $(NH_2CH_2)_2$/BuOH/THF	44	[18] [21]
Z-β^2hThr(^{t}Bu)-OH		**3**	1. H_2/Pd-C/THF 2. TFA/CH_2Cl_2 3. Z-Cl/$NaHCO_3$/CH_2Cl_2 4. Isobutylene/CH_2Cl_2/H_2SO_4 5. Bu_4NOH/MeCN/H_2O	26	[21] [22]
Z-β^2hTrp(Boc)-OMe		**4**	1. BF_3 Et_2O/Et_3SiH/CH_2Cl_2 2. LiBr/DBU/MeOH 3. Boc_2O/DMAP/MeCN	70	[23]
Z-β^2hTyr(^{t}Bu)-OH		**2h**	1. TBAF/THF 2. Isobutylene/CH_2Cl_2/H_2SO_4 3. NaOH/THF/H_2O	52	[21]
Z-β^2hVal-OH		**2b**	LiOH/THF/H_2O	61	

Table 2. *X-Ray Crystal Structures* (MOLMOL Presentation), *Formulae, and Melting Points* (in parentheses) *of DIOZ Derivatives Prepared in the Course of β^2-Amino Acid Syntheses.* Starting materials **1**, primary products **2f**, **3**, **5**, intermediates **9**–**15** on the way to the β^2-amino acid derivatives, and other diphenyl-oxazolidinones **16**–**32** prepared for β-amino acid syntheses will be described in separate forthcoming papers. The 3-nitro-2-methylpropanoyl-DIOZ derivative **24** and the imine **26** were prepared by Dr. *E. Otchertianova*, the *N*-nitroso-oxazolidinone **27** by Dr. *F. Rossi*. Color code: N: blue, O: red, S: yellow, F: green, Cl: magenta, Br: dark green, C and bonds: gray. Remarkably, the conformation around the Me_2CH-CH bond is identical in all 31 structures shown: the tertiary H-atom of the i-Pr group points towards the neighboring *quasi*-equatorial Ph group. Thus, as pointed out previously, the i-Pr group mimicks a *t*-Bu group, as far as facial bias of trigonal centers of substituents at C(3) of the oxazolidinone is concerned (*cf.* the discussion and a superposition of 27 structures in [13]). The crystal structure of (*S*,*S*)-*N*-Z-β^2hIle-OH (see *Table 1*) has also been determined. The data sets of the structures shown in this *Table* have been deposited with the *Cambridge Crystallographic Data Center*.

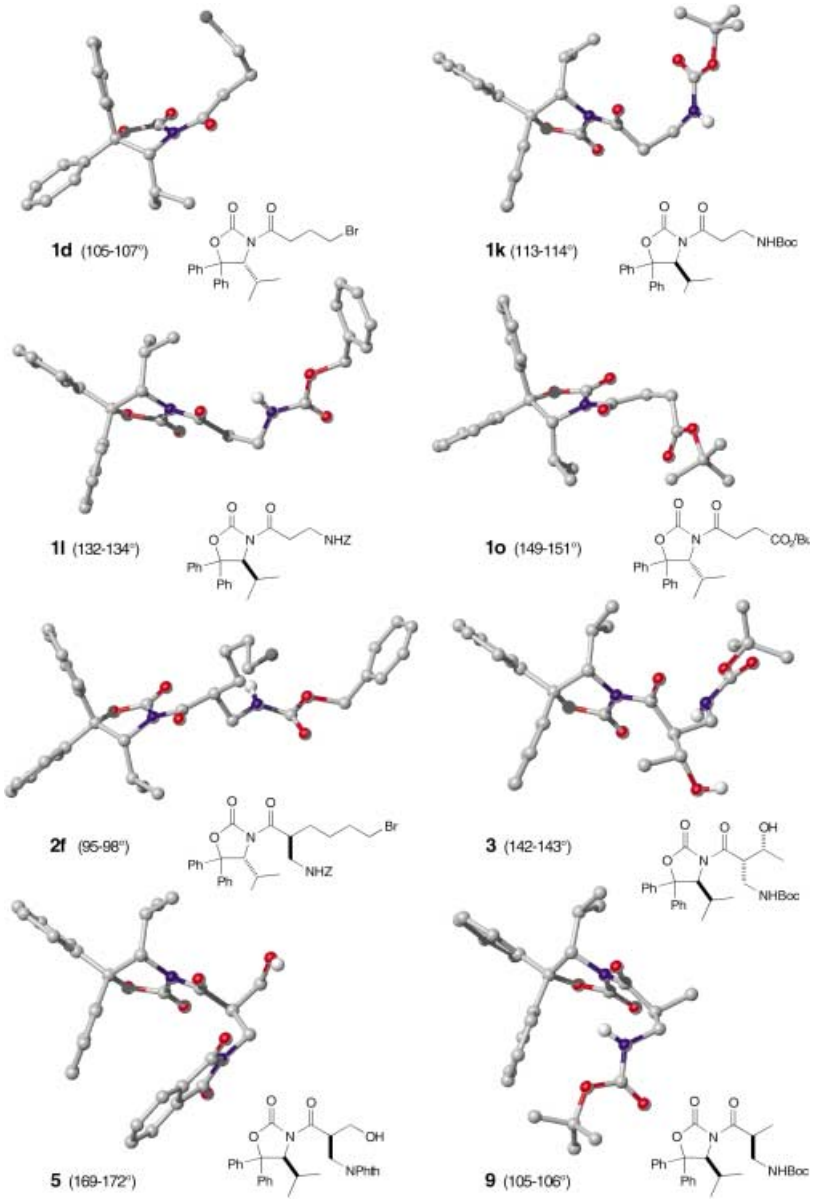


Table 2 (cont.)

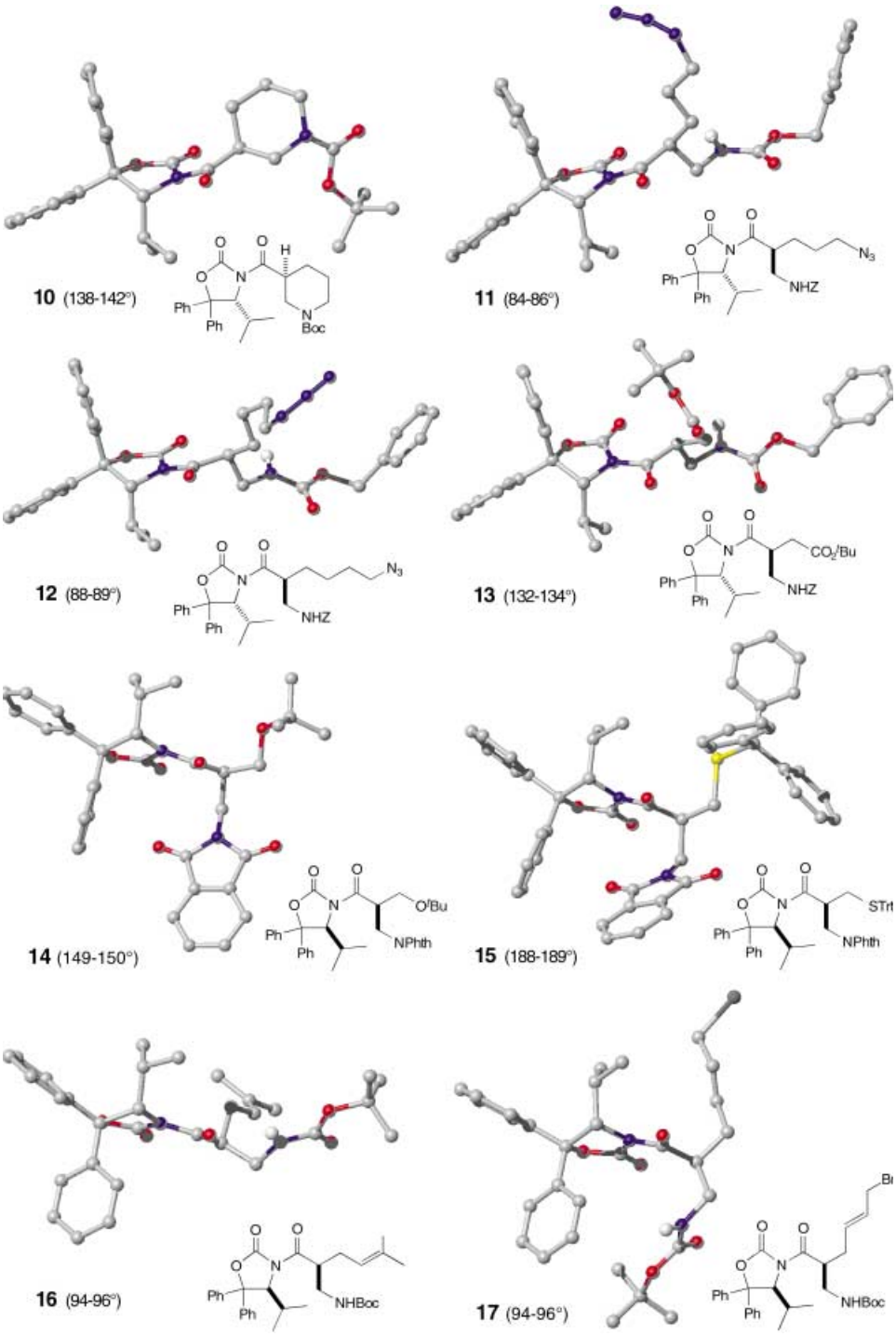
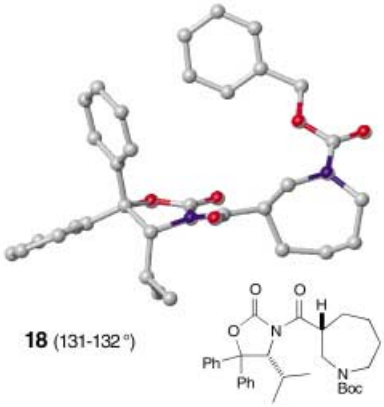
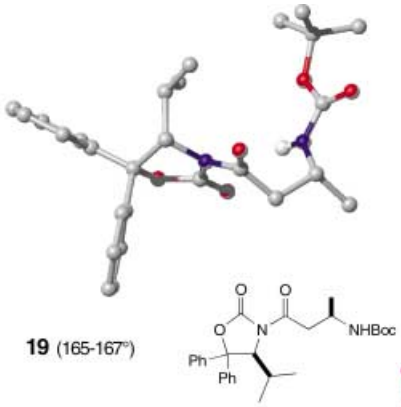

10 (138-142°)
11 (84-86°)
12 (88-89°)
13 (132-134°)
14 (149-150°)
15 (188-189°)
16 (94-96°)
17 (94-96°)

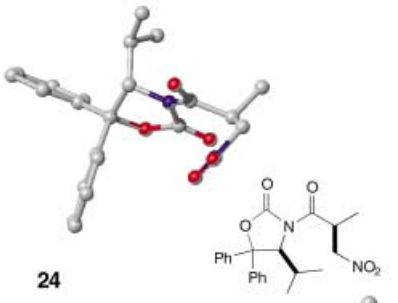
Table 2 (cont.)



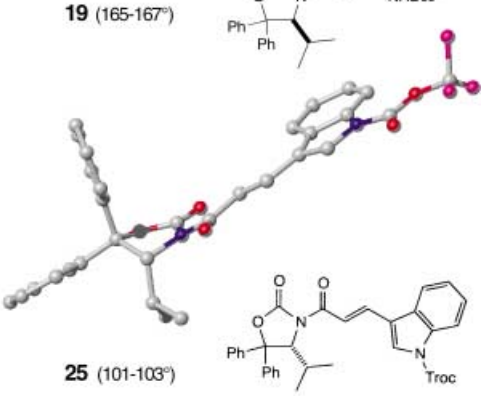
18 (131-132°)



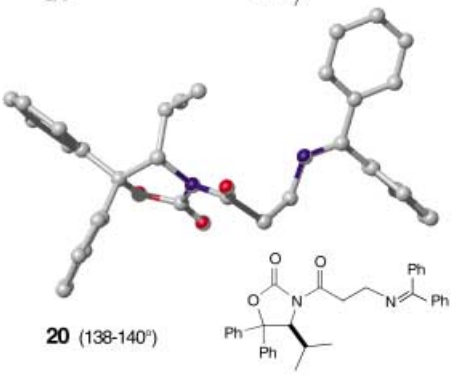
19 (165-167°)



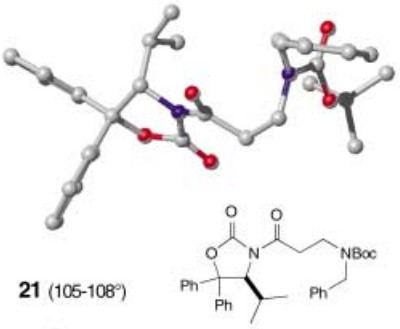
24



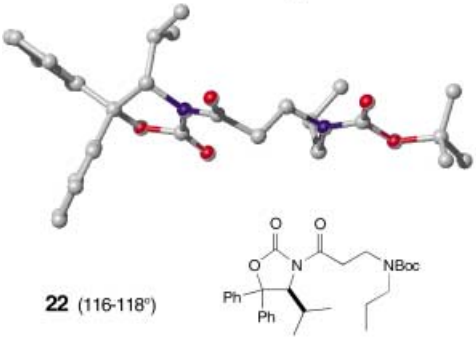
25 (101-103°)



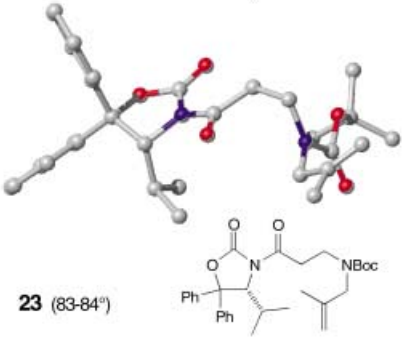
20 (138-140°)



21 (105-108°)

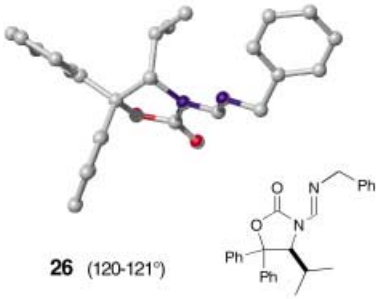


22 (116-118°)



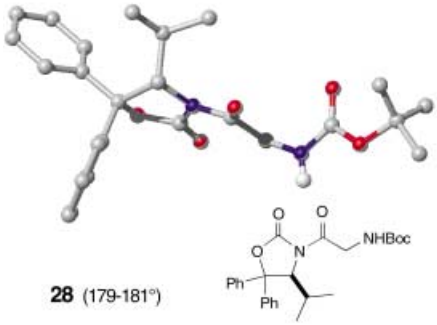
23 (83-84°)

Table 2 (cont.)

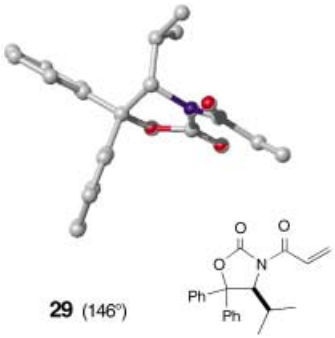


26 (120-121°)

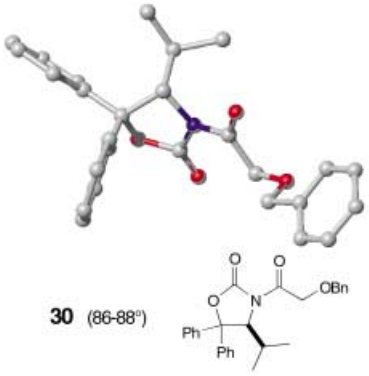
27 (143-145°)



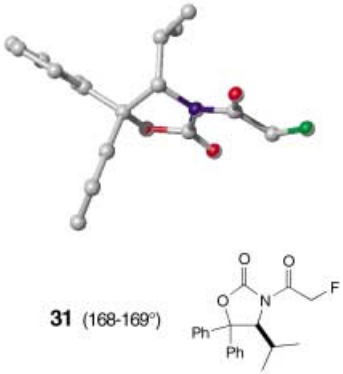
28 (179-181°)



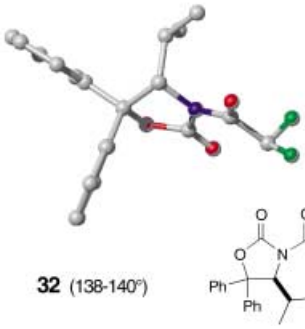
29 (146°)



30 (86-88°)



31 (168-169°)



32 (138-140°)

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