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1,3-DIPOLAR CYCLOADDITIONS OF 2-*tert*-BUTOXYCARBONYL-1-PYRROLINE *N*-OXIDE WITH CHIRAL ACRYLATES AND ACRYLAMIDES

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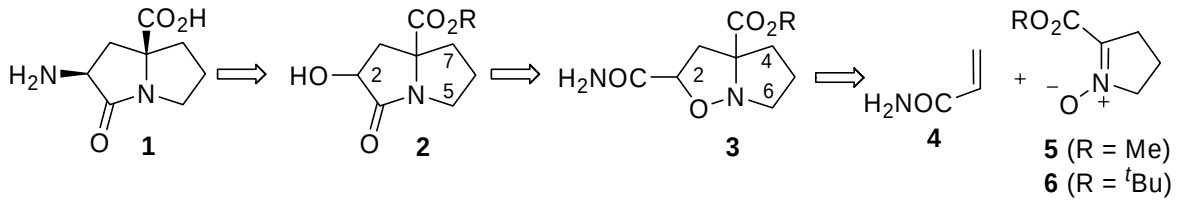
Dedicated to professor Barry Trost on the occasion of his 65th birthday

Abstract – The 1,3-dipolar cycloadditions of a series of chiral acrylates and acrylamides with 2-*tert*-butoxycarbonyl-1-pyrroline *N*-oxide were studied. The synthesis of enantiopure *tert*-butyl (2*R*,7a*R*)- and (2*S*,7a*S*)-2-hydroxy-3-oxo-tetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylates starting from the acryloyloxazolidinone derived from (*S*)-phenylalanine is reported.

INTRODUCTION

The pyrrolizidinone derivative (**1**) and its enantiomer are rigid Gly-(*s*-*cis*)Pro dipeptide surrogates able to mimic the two central residues of a β-turn.[1] The bicyclic skeleton of **1** was assembled by 1,3-dipolar cycloaddition (1,3-DC) of nitrone (**5**) or (**6**) derived from proline ester with acrylamide (**4**), followed by hydrogenolysis of the N-O bond of the adduct that allows *in situ* lactamization to afford 2,7a-disubstituted pyrrolizidinone (**2**). Both *cis*- and *trans*-**2** derived from *endo*- and *exo*-adducts (**3**), respectively, could be converted into the *cis*-amino acid (**1**) by stereoselective functional group interconversions (Scheme 1).[1]



Scheme 1.

Enantiopure **1** were obtained by insertion of a chiral auxiliary in a late step of the synthesis followed by separation of the diastereomeric intermediates, such as Mosher's esters[1c] or 1-phenylethylamines,[1b,1d] and removal of the chiral auxiliary.

As part of our ongoing work on the development of strategies for the preparation of enantiopure **1**, we explored the possibility of using a chiral acrylate or acrylamide to induce asymmetry in the very first step of the synthesis. Here we report the 1,3-DC of a series of enantiopure acryloyl derivatives with nitrone (**6**) and the synthesis of enantiopure *cis*-**2** (R = *t*-Bu) starting from the acryloyloxazolidinone derived from (*S*)-phenylalanine.

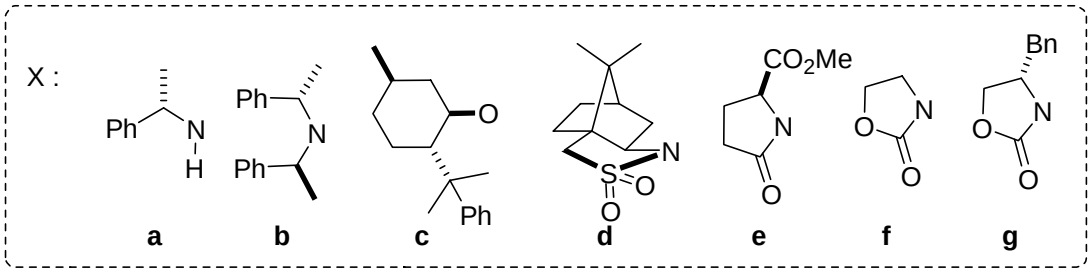
RESULTS AND DISCUSSION

To the best of our knowledge, there are only three previous reports on 1,3-DC of chiral acryloyl derivatives with cyclic nitrones (pyrroline *N*-oxide and 5,5-dimethylpyrroline *N*-oxide)[2] and slightly more examples with acyclic nitrones.[3] Literature data show a large dependence of regio- and stereoselectivity on the chiral auxiliary, the nitrone structure and the reaction conditions used, and lack of sufficient breadth to suggest a reliable chiral auxiliary for the acrylic component in the 1,3-DC with **6**. Accordingly, to our purpose it was necessary to test some of the most common amine, alcohol and amide chiral auxiliaries which are commercially available in enantiopure form (Table 1).

Regioisomeric and *endo*-*exo* diastereomeric ratios reported in Table 1 were generally determined by analysis of ^{1}H NMR spectra of the crude reaction mixtures.[4] The structure and relative configuration of the isomers were established by comparison of NMR spectral data with the corresponding adducts of **6** with **4**,[1d] and in some cases were validated through the spectral analysis of their products of hydrogenolysis (see below). Disappointingly, there was no significant asymmetric induction in any of these cycloadditions as all the isolated *endo* and *exo* adducts showed to be formed as a pair of diastereomers in roughly 1:1 ratio with the only exception of camphor sultam derivative (see below). The overall yields reported refer to material purified by chromatography on silica gel, but only few of the isomeric cycloadducts (**8-10**) could be completely separated. In general, the yields of cycloaddition were moderate to good due to the combination of low reactivity between the electron poor dipolarophiles and electron deficient nitrone, the tendency of some of the acrylates to polymerize under the reaction conditions, and the somewhat low stability of nitrone (**6**).

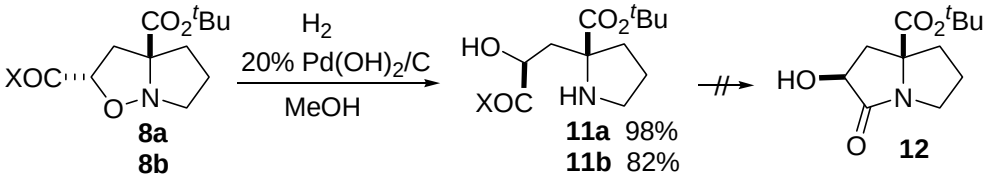
Treatment of nitrone (**6**) with acrylamides (**7a**)[5] and (**7b**)[6] afforded a complex mixture of cycloadducts including regioisomers (Table 1, entries 1 and 2). The major *endo* adducts (**8a-8b**) could be partially separated by chromatography on silica gel. Under the usual hydrogenolysis conditions, **8a** and **8b** afforded the corresponding monocyclic amino alcohols (**11a**) and (**11b**) which failed to cyclize to pyrrolizidinone (**12**) even under harsh conditions (Scheme 2).

Table 1. Reagents, products and reaction conditions of 1,3-DC reactions.



		Reaction	Regioisomeric Ratio	*endo*/*exo*	Yield[a]
	X	Conditions	(**8** + **9**) : **10**	**8**[b] : **9**	(%)
1	**a**	CH_2Cl_2, 40 °C, 10 h	77 : 23	64 : 36	85
2	**b**	CH_2Cl_2, rt, 3 d	86 : 14	66 : 34	87
3	**c**	CH_2Cl_2, rt, 4 d	73 : 27	100 : 0	68
4	**d**	CH_2Cl_2, 60 °C, 2 h[c]	67 : 33	87 : 13	74
5	**e**	CH_2Cl_2, rt, 4 d	69 : 31	100 : 0	75[d]
6	**f**	CH_2Cl_2, rt, 1 d	100 : 0	67 : 33	59
7	**f**	CH_2Cl_2, $MgCl_2$, rt, 1d[e]	100 : 0	55 : 45	56
8	**g**	CH_2Cl_2, rt, 5 d	100 : 0	63 : 37	34
9	**g**	CH_2Cl_2, 60 °C, 1 h[c]	100 : 0	75 : 25	49
10	**g**	H_2O, 64 °C, 14 h	100 : 0	73 : 27	36
11	**g**	CH_2Cl_2, $MgCl_2$, rt, 5d[e,f]	100 : 0	50 : 50	34
12	**g**	Cat, CH_2Cl_2, rt, 7 d[g]	100 : 0	75 : 25	60

a) Overall yield after chromatography on SiO_2. b) The diastereomeric ratio of isolated *endo*-adducts (**8**) were found 1:1 except for entry 4 [(*R*,*R*)-**8d** : (*S*,*S*)-**8d'** = 77:23] and entry 5 [(*S*,*S*)-**8e** : (*R*,*R*)-**8e'** = 60:40]. c) Microwave heating (150 W). d) Yield based on recovered **6** (62% conversion). e) 1 Molar equiv. of $MgCl_2$ was added. f) MeOH was added as cosolvent. g) Cat: Mg(II)-phenantroline complex (10 mol %), 4 Å MS (see ref. 17).



Scheme 2.

The relative and absolute configuration of one of the adducts (**8b**) was indirectly confirmed by single-crystal X-Ray analysis of the corresponding amino alcohol (**11b**) (Figure 1).[7]

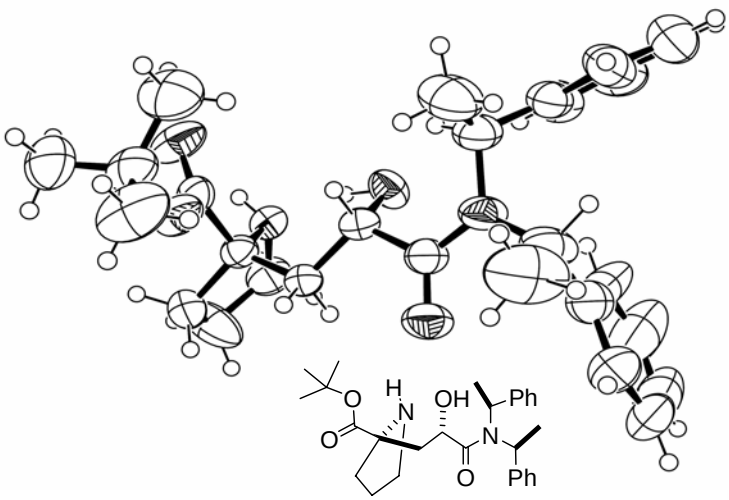
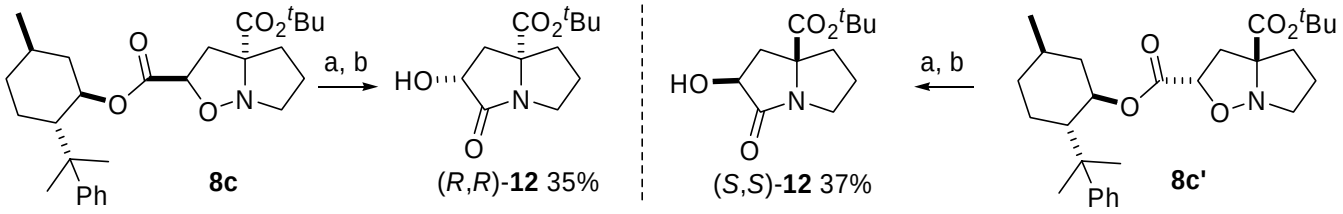


Figure 1. ORTEP representation of (*S*,*S*,*S*,*S*)-**11b**.

8-Phenylmenthyl acrylate (**7c**)[8] was more selective and afforded a mixture of two pair of regioadducts likely deriving from an *endo* approach between the reagents (Table 1, entry 3). One of the 2-menthyloxycarbonyl adduct (**8c**) could be isolated pure by chromatography (silica gel, eluent: petroleum ether/diethyl ether, 3:1) in 28% yield.

The hydrogenolysis/cyclization of isoxazolidines (**8c**)[9]and (**8c'**) was sluggish and required high temperatures (refluxing xylenes, 3.5 h) to go to completion, affording the enantiopure *cis*-substituted pyrrolizidinones (**12**) in unsatisfactory yields (35-37%) (Scheme 3). The *cis* configuration of the products (**12**) proved the *endo* geometry of the pyrrolo[1,2-*b*]isoxazolidines (**8c**), and ^{1}H NMR spectral analysis of their Mosher's esters allowed to assign the absolute configuration of both the enantiomeric alcohols (**12**)[1c] and the corresponding adducts (**8c**) and (**8c'**).

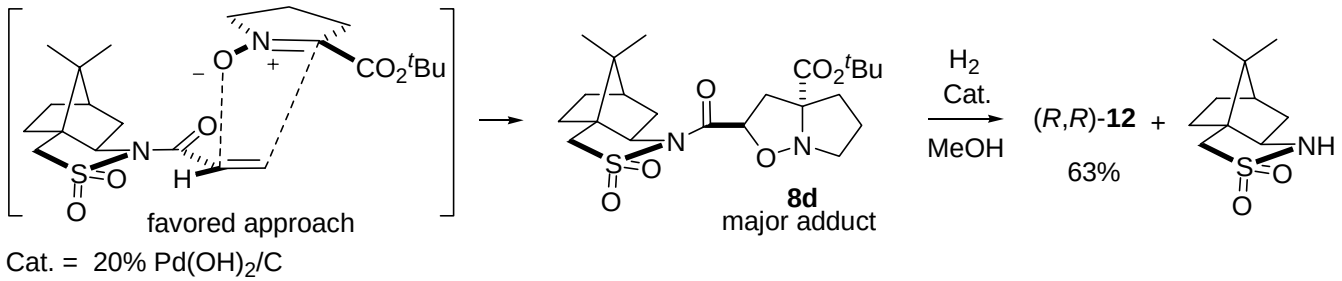


Scheme 3. a) H_2, 20% $Pd(OH)_2$/C, MeOH. b) Xylenes, reflux, 3.5 h

The cycloaddition of nitrone (**6**) with Oppolzer's sultam derivative (**7d**)[10] yielded a complex mixture of *endo* and *exo* stereoisomers (**8d**) and (**9d**) along with regioisomers (**10d**) (Table 1, entry 4). Acrylamide (**7d**) was the most diastereofacial selective dipolarophile studied as it afforded the two *endo* adducts (**8d**) and (**8d'**) in 77:23 ratio. Hydrogenolysis of major adduct (**8d**)[11] gave alcohol [(*R*,*R*)-**12**] in 63% yield and the chiral auxiliary could be recovered in high yields (Scheme 4). The *R* absolute configuration of the C-2 and C-3a stereocenters in the major adduct (**8d**) is in accord with the favored "top side" attack of nitrone (**6**) to the *s-cis* rotamer of **7d** as already observed in the thermal 1,3-DC with nitrile oxides[12] and acyclic nitrones.[3b,3d,3g]

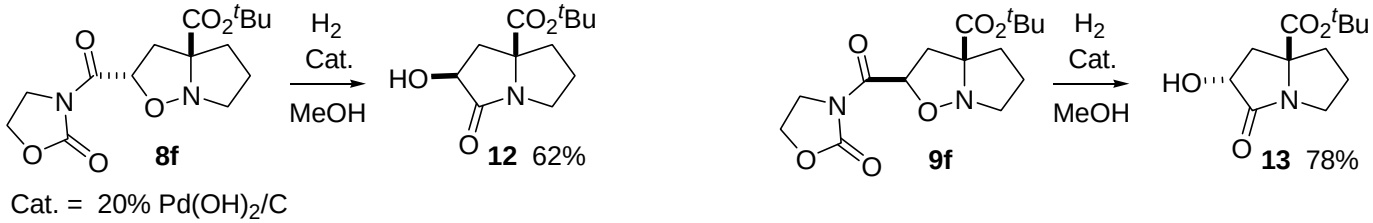
Similarly to **7c**, the chiral acrylamide (**7e**)[13] derived from (*S*)-pyroglutamic acid was completely *endo*-selective and afforded two pairs of *endo*-regioisomers (**8e-8e'**) and (**10e-10e'**) in 69-31 ratio (Table 1,

entry 5). Adducts (**8e**) and (**8e'**) could not be separated by chromatography on silica gel, and were converted into scalemic *cis*-pyrrolizidinone (**12**) (20% ee) by hydrogenolysis (81% yield). On the contrary, the two regioadducts (**10e**) and (**10e**') were isolated in pure form. The X-Ray analysis of one of them[7,14]confirmed the *trans* relationship between the two substituents due to the *endo*-approach between the reagents.



Scheme 4.

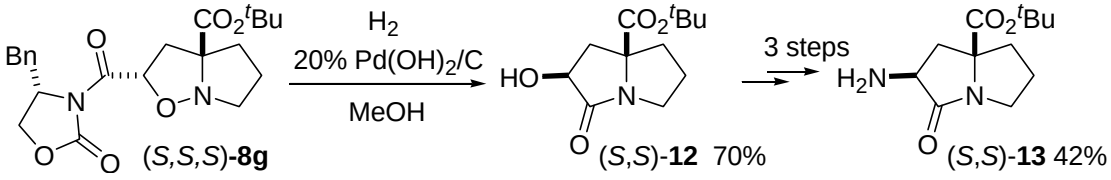
Hydrogenolysis of adducts (**8a-8e**) proved that the nature of the chiral auxiliary is also crucial in the cyclization step to the pyrrolizidinone. Therefore, before using the enantiopure (4*S*)-4-benzyl-1,3-oxazolidin-2-one as chiral auxiliary, the two step sequence, 1,3-DC and hydrogenolysis, was tested on the achiral 3-acryloyl-1,3-oxazolidin-2-one (**7f**).[15] The cycloaddition of **6** with **7f** was completely regioselective and slightly diasteroselective in favor of the *endo* adduct (**8f**) (Table 1, entry 6). The presence of a stoichiometric amount of $MgCl_2$ reduced the diastereoselectivity affording similar amount of **8f** and **9f** (Table 1, entry 7). The easily separable adducts (**8f**) and (**9f**) smoothly underwent hydrogenolysis/cyclization to racemic pyrrolizidinones (*cis*-**12**) and (*trans*-**13**), respectively (Scheme 5).



Scheme 5.

Analogously to **7f**, the cycloaddition of the chiral acryloyl oxazolidinone derived from (*S*)-phenylalanine (**7g**)[16] gave a mixture of four products with complete regioselectivity. The *endo* and *exo* adducts (**8g**) and (**9g**) were formed in 67/37 ratio (Table 1, entry 8), and each *endo*/*exo* diastereomeric pair consisted of equimolar amounts of two stereoisomers (**g**/**g'**). The variation of some of the experimental conditions moderately affected the *endo/exo* selectivity and the cycloaddition yield (Table 1, entries 8-12). The highest overall yield (60%) was obtained in the presence of a catalytic amount (10 mol%) of Mg(II)-phenantroline

complex and molecular sieves following the procedure reported by Jørgensen et al,[17] however without any effect on diastereoselectivity. The four adducts were partially separable by column chromatography with the following elution order: **9g** (7%), **9g'** + **8g'** (30%) and **8g** (23%) (silica gel, eluent: petroleum ether / ethyl acetate, initially 2:1 then 1:1).[18] The pure adduct (**8g**) underwent hydrogenolysis/cyclization at room temperature to afford (*S*,*S*)-**12** in 70% along with the chiral auxiliary (Scheme 6). Analogously, the mixture of **9g'** + **8g'** afforded, after hydrogenation and separation of the major diastereomer, the enantiomer (*R*,*R*)-**12**. As previously described, the optical purity and the absolute configuration of **12** were determined by analysis of the corresponding Mosher's esters.



Scheme 6.

Racemic **12** has been previously converted to the bicyclic amino ester (**13**) in three steps and 42% overall yield (Scheme 6).[1d] Accordingly, the preparation of (*S*,*S*)-**12** and (*R*,*R*)-**12** from nitrone (**6**) and chiral acrylate (**7g**), represents a new formal synthesis of both the enantiomers of **13** in 5 synthetic steps and 7% yield. The previous described strategy,[1d] which involves the use of 1-phenylethylamine as chiral auxiliary in a late step of the synthesis, affords both (*S*,*S*)-**13** and (*R*,*R*)-**13** in 5 synthetic steps in 4% yield each. Considering the chiral auxiliary cost, the number of synthetic steps and the overall chemical yield, these two approaches are equivalent and can equally be used in laboratory-scale preparations of enantiopure derivatives of **1.**

In conclusion, the 1,3-DC of cyclic nitrone (**6**) with several chiral acrylates and acrylamides followed by hydrogenolysis of cycloadducts was studied. The regio- and diasteroselectivity was strongly dependent on the chosen chiral auxiliary even if a substantial *endo* selectivity was generally detected, likely due to the favored secondary orbital interactions of acrylates in this approach, here enhanced by the steric interactions induced by the bulky CO_2tBu group on the nitrone in the *exo* approach. (Scheme 7).

No significant facial diasteroselectivity was observed, except with acryloylcamphorsultam (**7d**), which afforded the two *endo* stereoisomers (**8d**) and (**8d'**) in 3.3:1 ratio. Unfortunately dipolarophile (**7d**) resulted less regioselective. Acrylates (**7c**) and (**7e**) afforded both the regioisomeric adducts with complete *endo*-selectivity, whereas **7g** underwent a regioselective, but poor *endo*-selective cycloaddition. The major *endo*-adducts (**8g**) and (**8g'**) were separated and converted into the enantiopure pyrrolizidinones (**12**), useful intermediates for the synthesis of Gly-(*s*-*cis*)Pro dipeptide mimetic (**1**).

Scheme 7.

ACKNOWLEDGEMENTS

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4. *1,3-DC General Procedure.* A 1 M solution of the nitrone (**6**) (1.1 equiv.) and dipolarophiles (**7**) (1 equiv.) in CH_2Cl_2 was stirred at rt until starting material was no longer detected by TLC. The solvent was removed under reduced pressure and the crude mixture was purified by chromatography on SiO_2.
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9. (*R*,*R*)-**8c:** $[\alpha]^{25}_{D}$ = –4.7º (c =0.35, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.29–7.25 (m, 4H), 7.16–7.11 (m, 1H), 4.83 (td, *J* = 10.7, 4.4 Hz, 1H), 3.98 (dd, *J* = 8.6, 7.4 Hz, 1H), 3.37 (ddd, *J* = 12.7, 6.9, 4.2 Hz, 1H), 3.13 (m, 1H), 2.87 (dd, *J* = 12.7, 7.4 Hz, 1H), 2.25–1.80 (m, 8H), 1.64–1.54 (m, 2H), 1.48 (s, 9H), 1.31 (s, 3H), 1.22 (s, 3H), 1.01–0.97 (m, 2H), 0.88–0.82 (m, 1H), 0.86 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR (50 MHz) δ 171.2 s, 169.1 s, 150.5 s, 127.6 d, 2C, 125.1 d, 2C, 125.0 d, 81.6 s, 78.3 s, 76.9 d, 75.6 d, 56.9 t, 49.7 t, 42.5 t, 41.1 t, 39.6 d, 34.6 t, 34.1 t, 31.0 t, 27.6 q, 3C, 26.7 q, 26.5 q, 26.4 d 23.7 s, 21.5 q. [(*S*,*S*)-**8c'**] was obtained in mixture with regioisomers (**10c**)
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14. (3*R*,3a*S*)-**10e:** $[\alpha]^{20}_{D}$ = –22.8º (c = 1.1, $CHCl_3$); ^{1}H NMR (200 MHz) δ 4.79 (dd, *J* = 6.8, 4.2 Hz, 1H), 4.72 (dd, *J* = 9.2, 3.0 Hz, 1H), 4.44 (dd, *J* = 8.8, 4.0 Hz, 1H), 4.05 (dd, *J* = 8.6, 6.8 Hz, 1H), 3.77 (s, 3H), 3.25–3.19 (m, 1H), 3.08–2.99 (m, 1H), 2.77–2.33 (m, 4H), 2.28–1.80 (m, 4H), 1.52 (s, 9H); ^{13}C NMR (50 MHz) δ 174.1 s, 171.2 s, 2C, 171.1 s, 81.6 s, 80.6 s, 68.9 t, 58.1 d, 55.9 q, 55.5 t, 52.7 d, 31.7 t, 29.0 t, 27.8 q, 3C, 24.8 t, 21.6 t.
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18. (*S*,*S*,*S*)-**8g:** $[\alpha]^{25}_{D}$ = –2.6º (c = 1.13, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.37–7.17 (m, 5H), 5.48 (dd, *J* = 9.0, 7.4 Hz, 1H), 4.73–4.64 (m, 1H), 4.32–4.26 (m, 1H), 4.22 (dd, *J* = 9.1, 2.7 Hz, 1H), 3.55–3.48 (m, 1H), 3.37 (dd, *J* = 12.5, 7.3 Hz, 1H), 3.29 (dd, *J* = 13.3, 3.4 Hz, 1H), 3.22 (dd, *J* = 12.9, 1.8 Hz, 1H), 2.80 (dd, *J* = 13.4, 9.5 Hz, 1H), 2.35–2.26 (m, 1H), 2.23–2.13 (m, 1H), 2.18 (dd, *J* = 12.6, 9.0 Hz, 1H), 2.01–1.84 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (100 MHz) δ 171.6 s, 170.0 s, 152.6 s, 134.9 s, 129.4 d (2C), 128.9 d (2C), 127.5 d, 82.1 s, 78.7, s, 76.5 d, 67.0 t, 57.3 t, 55.2 d, 43.8 t, 37.8 t, 34.5 t, 27.8 q, 24.0 t.