Chiral Version of the Burgess Reagent and its Reactions with Epoxides

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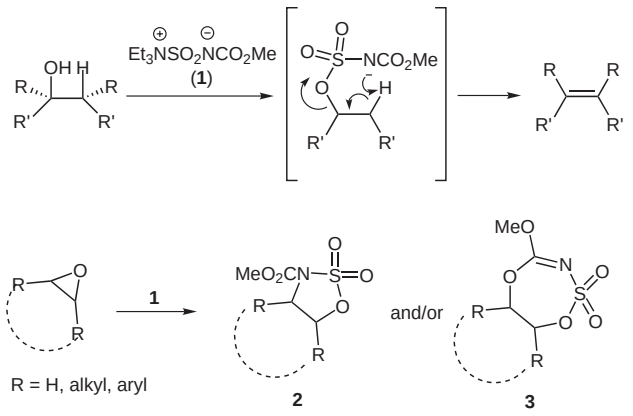
Abstract: A chiral auxiliary version of the Burgess reagent was prepared, and its reactions with epoxides were studied. Diastereomeric sulfamidates were converted to both enantiomers of protected *trans*-amino alcohols with ee of 84–98%.

Key words: chiral Burgess reagent, epoxides, menthol auxiliary group, sulfamidate, *trans*-amino alcohol derivatives

There has been a recent revival of interest in the chemistry of the Burgess reagent (**1**), originally designed and used for dehydration of alcohols.[1] Its reactivity with other functional groups has been reinvestigated.[2] Until recently it has been generally accepted that epoxides and many other functionalities are inert to treatment with the Burgess reagent.[3] In 2003 we published the first disclosure of reactions of epoxides with the Burgess reagent and demonstrated their conversion to five- and seven-membered sulfamidates of type **2** and **3**, respectively,[4] as shown in Scheme 1.



Scheme 1 Reactivity of the Burgess reagent with alcohols and oxiranes.

Nicolaou has demonstrated the conversion of diols and other functionalities to sulfamidates, carbamates, and other compounds.[5] We have proposed a common mechanism and have indicated the possibility of degenerate pathways to the sulfamidate from both epoxides and diols.[4] Although an earlier report suggested that aryl-substituted diols provided a regioisomeric mixture of five-membered ring sulfamidates,[5b] we have shown that styrene diol, styrene oxide and other aryl-substituted oxiranes produce rather the seven-membered sulfamidate of type **3** as major products.[4] These observations were subsequently acknowledged in a recent paper by Nicolaou,[5c] who showed that the production of seven-membered sulfamidates is a function of the electron density of the aromatic ring, which invites the reactivity of the resonance form of the Burgess reagent **1b** (Figure 1).

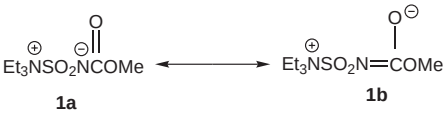


Figure 1

The anion localized on oxygen, as in **1b**, clearly prefers the 'harder' benzylic site in aryl-substituted oxiranes, and hence these reactions lead predominantly to seven-membered sulfamidates **3**.

Since the reactive options of the Burgess reagent seem to be subject to electronic control and can therefore be modulated, we have chosen to test several asymmetric versions of the reactions with oxiranes. Chiral catalysts were tested with *meso*-epoxides and achiral Burgess reagent for asymmetric induction. A chiral auxiliary version of the reagent was prepared with the expectation that both enantiomers of amino alcohols would be obtained, following separation and removal of the auxiliary group. There are many examples in the literature of asymmetric reactions of *meso*-epoxides catalyzed by various C_2-symmetric Lewis acids.[6] We tested two such catalysts: Jacobsen's[7] salen catalyst (**4**) and Bolm's[8] scandium triflate catalyst (**5**, Figure 2). In both cases, racemic products were obtained from cyclohexene oxide.

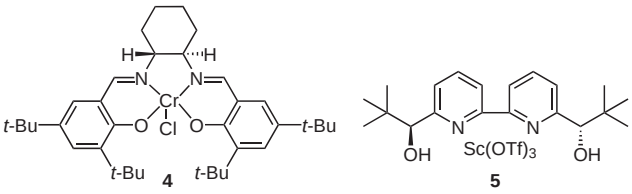


Figure 2

One possible explanation of the complete lack of asymmetric induction in this reaction may be that the Burgess reagent itself may act as a Lewis acid and displace the ac-

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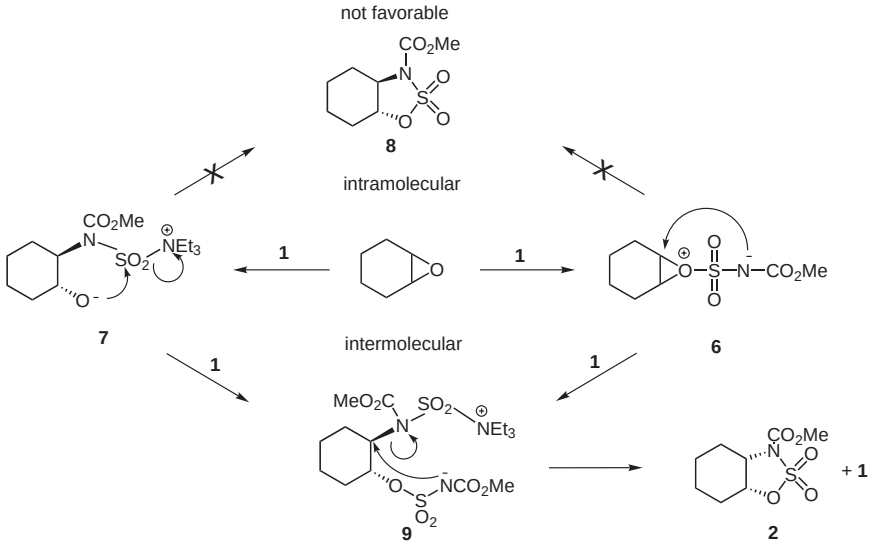


Scheme 2 Possible mechanistic options for the formation of *cis*-sulfamidates from epoxides.

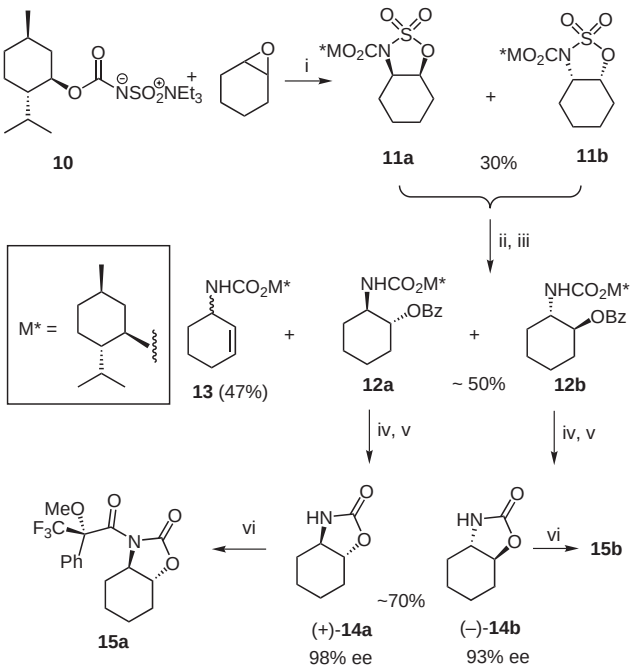
tual catalyst from the activated epoxide. As the reagent is used in more than stoichiometric quantities (2.3 equiv) and the concentration of the catalyst is only 10 mol%, the competition is unfavorable for the development of a chiral transition state. This suspicion is supported by preliminary calculations.[9] At this stage of the project we have also noted that the sulfamidates **2** are *cis*-, not *trans*-fused as we originally reported in our 2003 publication.[4] The *cis* stereochemistry is clearly a consequence of the mechanism of this reaction and the requirement of two equivalents of the reagent, one of which returns unchanged into the reaction cycle.

Possible mechanistic options are shown in Scheme 2. Two different pathways of the reaction for oxiranes with the Burgess reagent are possible. The activation of the epoxide to give compound **6** is likely and supported by preliminary calculations.[9] Another option is the direct nucleophilic attack of the Burgess reagent yielding compound **7** although this process has a higher activation energy than the formation of **6**.[10] In either case, an intramolecular closure to the sulfamidate is rather unlikely; a more plausible mechanism invokes the reaction of either **6** or **7** with a second equivalent of the Burgess reagent. Rather than ejecting triethylamine by an intramolecular sulfonation, alkoxide **7** reacts with the second equivalent of the reagent to produce **9**, also formed from the opening of activated epoxide **6**. Displacement of the Burgess reagent then occurs from the site of initial oxirane opening. A similar mechanism has also been proposed for the reaction of (**1**) with diols and we have shown that epoxides may be intermediates in these reactions.[4,5c] A study of concentration- and stoichiometry-dependence indicated that indeed at least two equivalents are essential; with one equivalent of the reagent yields were halved. Dilution experiments did not change the product content.

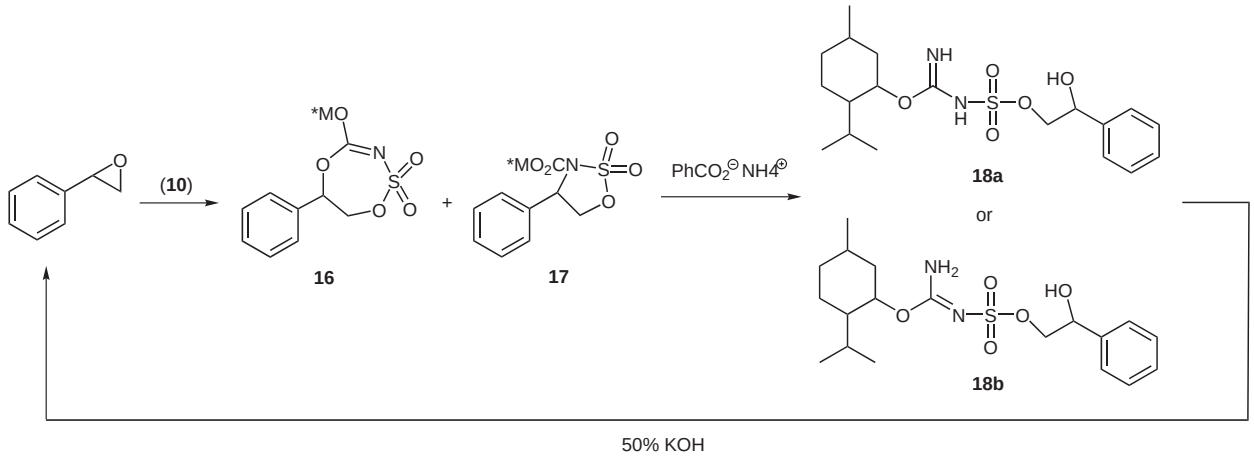
Surprised that the two C_2-symmetric catalysts proved to be completely ineffective in these reactions, we therefore turned to the chiral-auxiliary-based approach, recognizing that in this fashion both enantiomers of the products can be obtained and converted to valuable amino alcohol derivatives (both *cis* and *trans*), whose use is common in medicinal chemistry.[11]

A menthol version of the Burgess reagent was prepared and reacted with cyclohexene oxide producing a 1:1 mixture of diastereomers of *cis*-fused sulfamidates as shown in Scheme 3.

The separation of diastereomers **11a** and **11b** was arduous, and the mixture was converted to benzoates **12a** and **12b** with ammonium benzoate. Because the sulfamidates resemble cyclic sulfates in their reactivity with nucleo-

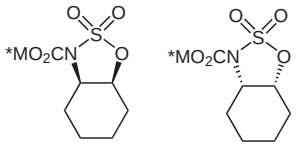
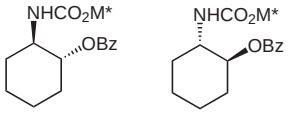
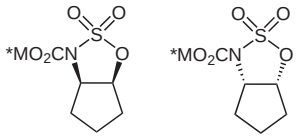
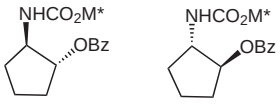
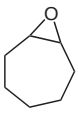
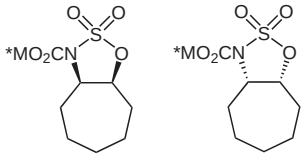
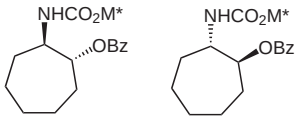
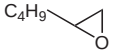
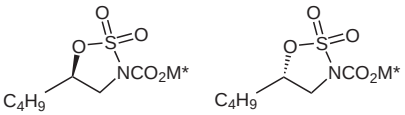
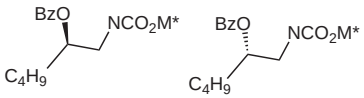
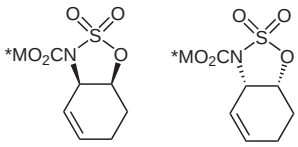
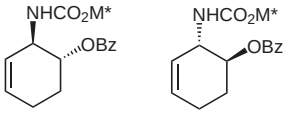


Scheme 3 *Reagents and conditions*: i. THF reflux, 1.5 h; ii. $PhCO_2^-NH_4^+$, DMF, 45 °C, 12 h; iii. THF, H_2O, concd H_2SO_4, r.t., 6 h; iv. 1 M NaOH in MeOH, 2 h; v. NaH, THF reflux, 18 h; vi. *n*-BuLi, 0 °C, 30 min, Mosher's acid chloride, –78 °C to r.t.



Scheme 4 Formation of sulfonyl urea derivative **18**.

Table 1 Reactions of Oxirane with Menthyl Version of the Burgess Reagent

Oxirane	Sulfamidates (%)[a]	Benzoates (%)	ee (%)[b] or de (%)[c]
	 **11a** **11b** 30%	 **12a** **12b** 49%	(+) 98 and (–) 93[b]
	 **19a** **19b** 37%	 **20a** **20b** 52%	98 and 93[c]
	 **21a** **21b** 35%	 **22a** **22b** 75%	93 and 92[c]
	 **23a** **23b** 22%	 **24a/24b**[d] 36%	–
	 **25a** **25b** 36%	 **26a** **26b** 51%	(+) 94 and (–) 84[e]

[a] Yields are isolated and unoptimized.
[b] Enantiomeric excess determined by Mosher's amide formation of cyclic carbamates, derived from the corresponding benzoates by hydrolysis and cyclization.
[c] Diastereomeric excess determined by GC/MS of benzoates after separation by flash column chromatography.
[d] Not separable by flash column chromatography.
[e] Diastereomeric excess determined by GC/MS of separated benzoates after hydrogenation.

philes this process also allows for the synthesis of *trans*-amino alcohols. Separation of the benzoates and conversion to the known cyclic carbamates **14a** and **14b** provided evidence of excellent enantiomeric excess in both amino alcohol products {optical rotations of **14a** and **14b** were higher than reported literature values: Compound **14a**: $[\alpha]_D^{22}$ +7.5 (*c* 1.0, EtOH), lit.[12] +6.0 (*c* 1.0, EtOH); compound **14b**: $[\alpha]_D^{22}$ –7.4 (*c* 1.0, EtOH), lit.[12] –5.9 (*c* 1.0, EtOH)}. Accurate determinations of enantiomeric purity were made by ^{19}F NMR evaluation of Mosher amides **15a** and **15b** and comparison with Mosher amide data obtained on the racemate of **14**. A moderate yield of the allylic amine derivative **12** was obtained from the reaction of sulfamidates **11a** and **11b** with ammonium benzoate. A more detailed study of this reaction revealed that treatment of **11a** and **11b** under strongly acidic conditions (6 N HCl–dioxane, 1:1) led to the isolation of racemic **13** in nearly quantitative yield. Simply heating a mixture of **11a** and **11b** in DMF at 45 °C for 18 hours provided **13** in moderate yield (55%) along with recovered starting material. This is another useful result as it allows for the direct conversion of epoxides to derivatives of allylic amines. In cases where the diastereomers are more easily separated, both enantiomers of allylic amine carbamates will therefore become available.

The results from the reactions of other oxiranes with menthyl Burgess reagent **10** are summarized in Table 1. The moderate isolated yields of *cis*-sulfamidates reflect the difficulty of isolation and separation of the diastereomers, not an uncommon problem in auxiliary group-mediated resolutions.[13] These issues will eventually be addressed and solved by employing more rigid, bulkier auxiliary groups, such as those derived from pinene, sparteine, or quinine. We anticipate that the *cis*-fused sulfamidates will then be more easily separated and lead to optically active *cis*-amino alcohols through hydrolysis.

The *cis*-sulfamidates were converted to *trans*-benzoates via inversion with ammonium benzoate at the oxygenated carbon and the enantiomeric or diastereomeric excess was determined after separation by column chromatography. Benzoates **26a** and **26b** were hydrogenated to **12a** and **12b**, respectively, and their identity as well as their optical purity evaluated by direct comparison, establishing also that no allylic mode of the oxirane opening occurred. The products from the reactions of *n*-butyl oxirane proved unseparable.

As expected, the reaction of styrene oxide with the chiral Burgess reagent yielded predominately the seven-membered sulfimidate **16**, which was treated with ammonium benzoate to yield a mixture of diastereomers identified by 2D-NMR (gDQCOSY, gHMQC and gHMBC at –20 °C) tentatively as **18a** or **18b**,[14,15] apparently produced by the protonation of sulfimidate **16** and displacement with ammonia (Scheme 4). Attempts to hydrolyze the sulfonyl group under basic conditions resulted in the formation of racemic styrene oxide, in agreement with previous results.[4]

These initial results provide for the first example of the chiral version of the Burgess reagent and demonstrate that chiral derivatives of both *cis*- and *trans*-amino alcohols can be obtained from epoxides in an enantiodivergent fashion through resolution methodology. Future work will focus on the detailed mechanistic study of this reaction, reinvestigation of C_2-symmetric catalysts under stoichiometric or Lewis acid catalyzed conditions, and synthesis and exploration of other more rigid, chiral auxiliary groups, which will permit easier separation of diastereomeric sulfamidates. Application of this reaction will be extended to other reactive systems such as aziridines, and these results will be reported in due course.

Experimental Procedures

Determination of diastereomeric excess was performed on a Perkin Elmer Claurus 500 GC/MS using a Perkin Elmer Elite-5MS column, 10 m, 0.25 mmID, 2 mL/min helium flow. For the separation of diastereomers following temperature program was used 50 °C (2 min), 15 °C/min to 160 °C, 1 °C/min to 240 °C, 15 °C/min to 300 °C (3 min).

Menthol Burgess Reagent 10

A solution of menthol (5 g, 32 mmol) in dry benzene (15 mL) was added dropwise to a solution of chlorosulfonyl isocyanate (5.21 g, 36.8 mmol) in dry benzene (15 mL) over 20 min. The reaction temperature was kept between 25–30 °C using an ice-water bath. After complete addition, the reaction mixture was stirred at r.t. for an additional 30 min. The solvent was removed under reduced pressure and the residue was purified by crystallization (hexane, 40 mL) to give the menthol sulfamoyl chloride intermediate as colorless crystals (87%); mp 86–88 °C (hexane); $[\alpha]_D^{23}$ –64.5 (*c* 0.8, $CHCl_3$). To a solution of Et_3N (4.76 g, 47 mmol) in benzene (20 mL) was added dropwise a solution of menthol sulfamoyl chloride (7 g, 23.5 mmol) in dry benzene (40 mL) keeping the reaction temperature between 10–15 °C. After stirring at r.t. for 1 h, the reaction mixture was filtered. The solvent was evaporated and the residue was crystallized from THF–hexanes to give 7.24 g of menthol Burgess reagent **10** as colorless solid (85%); mp 87–89 °C (THF–hexanes); $[\alpha]_D^{23}$ –48.7 (*c* 0.475, $CHCl_3$). IR (film): ν = 3426, 3020, 2958, 2872, 1682, 1457, 1389, 1369, 1340, 1285, 1253, 1216, 1105, 982, 922, 891 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.51 (td, *J* = 11.0, 4.6 Hz, 1 H), 3.45 (q, *J* = 7.7 Hz, 6 H), 3.14–3.26 (m, 1 H), 1.93–2.08 (m, 2 H), 1.65 (d, *J* = 11.9 Hz, 2 H), 1.30–1.44 (m, 11 H), 0.92–1.03 (m, 2 H), 0.87 (t, *J* = 7.7 Hz, 6 H), 0.76 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.7, 76.4, 50.7, 47.3, 46.7. 41.3, 34.6, 31.8, 26.4, 23.7, 21.2, 16.6, 9.8, 8.8.

General Procedure for the Reaction of Oxiranes with Menthyl Burgess Reagent

To a solution of oxirane (2.0 mmol) in THF (5 mL) was added menthol Burgess reagent **10** (4.69 mmol). And the resulting reaction mixture was stirred at 70 °C until complete consumption of the oxirane (TLC). The reaction mixture was cooled to r.t. and filtered through a plug of silica to remove salts formed during the reaction. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (hexanes–EtOAc, 8:1) affording two diastereomers in a ratio of 1:1.

***trans*-1-(*N*-Carbomenthyloxy)-2-benzoylcyclohexane 12a and 12b**

To a solution of diastereomers **11a** and **11b** (170 mg, 0.47 mmol) in dry DMF (1 mL) was added ammonium benzoate (120 mg, 0.85 mmol). The solution was heated to 45 °C until TLC analysis indicated full conversion of the starting material (18 h). The solvent was evaporated and the residue was dissolved in THF (3 mL). Three

drops of H_2O and concentrated H_2SO_4 were added and the reaction mixture was stirred at r.t. for 12 h, before the pH was set to 8 (sat. $NaHCO_3$). The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with H_2O and brine and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2–MeOH, 400:1) affording 47 mg of **12a** (25%) and 46 mg of **12b** (24%).

Compound **12a**: mp 111–113 °C; R_f = 0.5 (CH_2Cl_2–MeOH, 100:1); $[\alpha]_D^{20}$ –77.8 (*c* 1.05, $CHCl_3$). IR: ν = 3434, 3368, 3019, 2954, 2868, 1711, 1603, 1585, 1513, 1452, 1370, 1318, 1279, 1216, 1115, 1038, 1028, 757, 712, 668 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 7.7 Hz, 2 H), 7.55 (t, *J* = 7.2 Hz, 1 H), 7.43 (t, *J* = 7.7 Hz, 2 H), 4.83 (dt, *J* = 10.6, 4.5 Hz, 1 H), 4.59 (d, *J* = 9.3 Hz, 1 H), 4.34–4.46 (m, 1 H), 3.76–3.90 (m, 1 H), 2.07–2.19 (m, 2 H), 1.73–1.93 (m, 3 H), 1.13–1.69 (m, 10 H), 0.91–1.06 (m, 1 H), 0.86 (d, *J* = 10.0 Hz, 3 H), 0.75 (d, *J* = 6.6 Hz, 3 H), 0.46–0.68 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 156.5, 133.4, 130.6, 130.2, 128.7, 76.6, 74.7, 54.3, 47.5, 41.2, 34.6, 32.8, 31.5, 26.6, 25.0, 24.5, 23.8, 22.2, 21.1, 16.8. HRMS: *m/z* calcd for $C_{24}H_{35}NO_4$: 401.2566; found: 401.2579.

Compound **12b**: mp 138–141 °C; R_f = 0.45 (CH_2Cl_2–MeOH, 100:1); $[\alpha]_D^{20}$ –15.8 (*c* 1.05, $CHCl_3$). IR (film): ν = 3685, 3435, 3020, 2956, 2869, 1711, 1515, 1452, 1318, 1279, 1216, 1115, 1039, 929, 759, 714, 669 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.7 Hz, 2 H), 7.55 (t, *J* = 7.1 Hz, 1 H), 7.43 (t, *J* = 7.7 Hz, 2 H), 4.86 (dt, *J* = 10.6, 4.5 Hz, 1 H), 4.69 (d, *J* = 9.3 Hz, 1 H), 4.35–4.49 (m, 1 H), 3.73–3.90 (m, 1 H), 2.12 (d, *J* = 12.5 Hz, 2 H), 1.98 (d, *J* = 11.9 Hz, 1 H), 1.73–1.88 (m, 2 H), 1.08–1.68 (m, 10 H), 0.79–0.97 (m, 5 H), 0.55 (d, *J* = 6.4 Hz, 3 H), 0.30 (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 156.3, 133.3, 130.4, 130.1, 128.7, 76.0, 74.6, 54.4, 47.6, 41.8, 34.6, 33.2, 31.7, 31.6, 26.5, 24.9, 24.5, 23.9, 22.4, 20.7, 16.3. HRMS: *m/z* calcd for $C_{24}H_{35}NO_4$: 401.2566; found: 401.2575.

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(14) Compound **18**: colorless oil; $[\alpha]_D^{23}$ –48.5 (*c* 0.275, $CHCl_3$). IR (film): ν = 3448, 3340, 2956, 2926, 2871, 1631, 1548, 1496, 1446, 1372, 1322, 1173, 1097, 986, 954, 917, 863, 815, 759, 700, 661, 609, 541 cm^{-1}. ^1H NMR (499 MHz, $CDCl_3$): δ = 7.28–7.46 (m, 5 H), 7.06 (br s, 1 H), 5.76 (br s, 1 H), 5.06 (dt, *J* = 9.3, 2.2 Hz, 1 H), 4.80 (td, *J* = 11.0, 4.6 Hz, 1 H), 4.24 (ddd, *J* = 10.6, 8.8, 2.8 Hz, 1 H), 4.13 (ddd, *J* = 18.2, 10.3, 9.2 Hz, 1 H), 2.68 (br s, 1 H), 2.08 (d, *J* = 12.5 Hz, 1 H), 1.83–1.91 (m, 1 H), 1.67 (d, *J* = 12.1 Hz, 2 H), 1.32–1.51 (m, 2 H), 0.99 (q, *J* = 11.6 Hz, 1 H), 0.91 (d, *J* = 5.8 Hz, 3 H), 0.89 (dd, *J* = 6.8, 1.0 Hz, 3 H), 0.85 (m, 1 H), 0.76 (t, *J* = 6.5 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.3, 138.5, 129.1, 128.7, 126.5, 79.5, 75.0, 72.1, 47.1, 40.7, 34.1, 31.5, 26.4, 23.3, 22.4, 21.2, 16.8. HRMS: *m/z* calcd for $C_{19}H_{30}N_2O_5S$: 398.1875; found: 398.1855.

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