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Studies on Ristocetin A. A Synthesis of Protected Ristomycinic Acid Using Organomanganese Chemistry.‡

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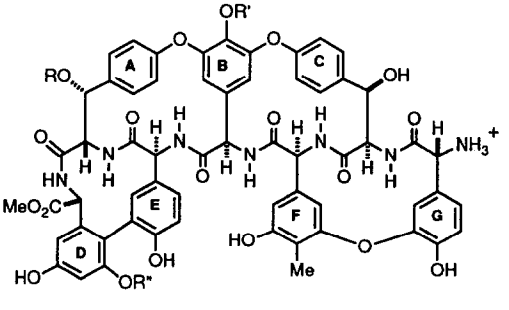
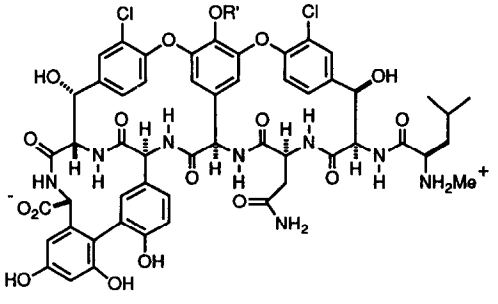
Abstract. Aryl ether formation by reaction of phenoxide nucleophiles with chloroarene-$Mn(CO)_3$ cationic complexes, followed by reaction of the aryloxyarene-$Mn(CO)_3$ complex with chiral glycine enolate equivalents, provides methodology for the synthesis of protected ristomycinic acid derivatives in a state of high optical purity.

Ristocetin A (**1**), a member of the group of glycopeptide antibiotics related to vancomycin (**2**),[1] presents a considerable challenge for the synthetic organic chemist, not least because the aryl ether linkages characteristic of this molecule must be constructed in the presence of arylglycine derivatives. Such compounds are prone to racemization under mildly basic conditions,[2] so that the usual methods for aryl ether construction, such as the Ullman coupling procedure,[3] may not be used, although this method has been applied to the preparation of aryl ethers of the isodityrosine type.[4] Evans *et al.*[5] and Suzuki *et al.*[6] have developed elegant approaches to the vancomycin skeleton based on a thallium (III)-promoted intramolecular oxidative coupling procedure to furnish the requisite aryl ethers. Our own work in this area aims at using a transition metal moiety to activate arenes toward nucleophilic addition, allowing the use of very mild reaction conditions to effect the construction of aryl ethers from arylglycine derivatives.[7] The present paper describes our expansion of these studies to the preparation of an F/G diaryl ether subunit for ristocetin A, which corresponds to a protected form of ristomycinic acid (**3**). We anticipate that such building blocks will ultimately find application in a projected total synthesis of ristocetin A.

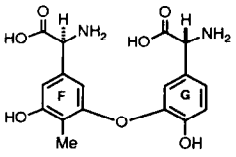


(1) **RISTOCETIN A** (R, R' and R" = sugar units)



(2) **VANCOMYCIN** (R' = sugar unit)

‡ Dedicated to Professor Charles Rees on the occasion of his retirement.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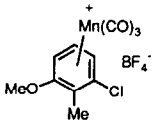
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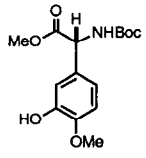
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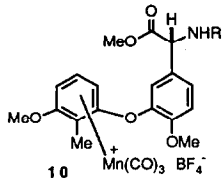
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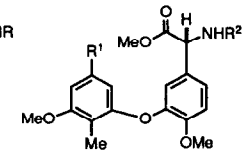
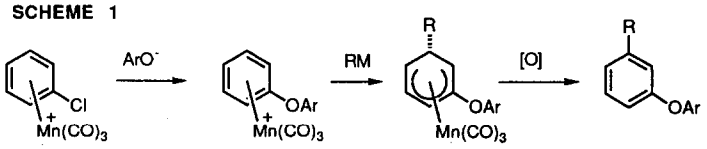

11 R' = CH(NHP)CO_2R

Results and Discussion.

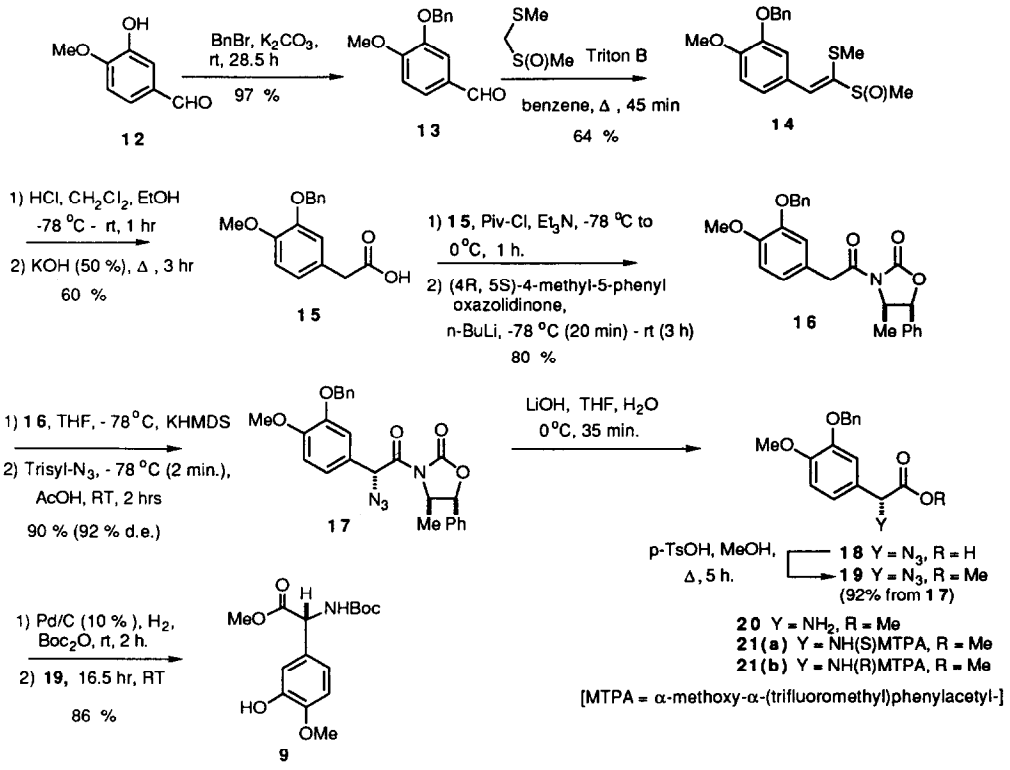
Arene-manganese tricarbonyl complexes are known[8] to be very reactive toward nucleophiles, allowing conversion of chloroarenes to diaryl ethers under exceptionally mild conditions (e.g., 0 °C, acetone, 5-10 min). Moreover, the product aryl ether manganese complexes undergo addition of carbanion nucleophiles to give cyclohexadienyl complexes which can be oxidatively demetallated to give regioselectively functionalized diaryl ethers. This overall procedure is illustrated in Scheme 1, which has been used as the basis for ongoing investigations in our laboratory on synthetic approaches to the vancomycin family.[7]

SCHEME 1


4 (BF_4^- or PF_6^-) 5 (BF_4^- or PF_6^-) 6 7

The construction of ristomycinic acid derivatives requires that the arene-$Mn(CO)_3$ complex **8** be coupled with the protected arylglycine **9** to give **10**, which is followed by the regio- and stereocontrolled introduction of the glycine side chain to give **11**. The work described herein parallels our synthesis of deoxyristomycinic acid derivatives reported earlier,[7(a)] which used commercially available 3-hydroxyphenylglycine. The requisite manganese complex **8** was reported in the earlier work, and is prepared by direct complexation of 3-chloro-2-methylanisole using $Mn_2(CO)_{10}$ and tetrafluoroboric acid in trifluoroacetic anhydride[9] (reflux, 16h). In the earlier work we found that better yields are obtained by treating the arene with $Mn_2(CO)_8Cl_2$ under the same reaction conditions but for a shorter reaction time (HBF_4, TFA anhydride, reflux 3h, 90% yield). While somewhat more convenient in terms of reaction time, it should be noted that the requisite octacarbonyldichlorodimanganese is itself prepared from $Mn_2(CO)_{10}$ in *ca* 91% yield by treatment with chlorine in carbon tetrachloride.[10] In the present work we have used $Mn_2(CO)_{10}$ directly, since the overall yield is the same.

The required arylglycine **9** was prepared as shown in Scheme 2, using the Evans asymmetric azidation procedure to introduce the amino group.[11] Isovanillin (**12**) was protected as its benzyl ether **13**, and this was homologated to the arylacetic acid **15** *via* the methylsulfinyl sulfide derivative **14**.[12] The hydrolysis of **14** to **15** was not straightforward, a modification of the literature procedure being required to give product with acceptable purity in respectable yield. This approach, however, is somewhat more convenient than the classical Arndt-Eistert homologation. Conversion of **15** to the oxazolidinone **16**, using the mixed anhydride method,[11] proceeded without problem, and azidation of **16** gave 90% yield of **17** obtained with a diastereomeric excess of 92% according to ^1H NMR spectroscopy. Crystallization from diethyl ether afforded diastereomerically pure material in 71% yield. Hydrolysis to the azido acid **18** was best accomplished using lithium hydroxide (25% H_2O in



SCHEME 2 Preparation of 3-Hydroxy-4-methoxyphenylglycine Derivatives

THF, 0 °C, 35 min), and the resulting acid was converted to the methyl ester **19** by Fischer esterification.

Treatment of **19** with hydrogen over 10% palladium on carbon catalyst, in the presence of Boc anhydride gave **9**, resulting from hydrogenolysis of the benzyl ether, reduction of azide, and *in situ* protection of the so-formed amine. The optical purity of a sample of **19** was determined by conversion to the MTPA amide derivatives[13] by treatment of the amino ester **20** with (+) and (-)-MTPA in the presence of diimide coupling reagents (see Experimental Section). ^{19}F NMR spectroscopy (Fig. 1) of the diastereomeric amides **21(a)** and **21(b)** indicated a ratio of *ca* 13:1, corresponding to an enantiomeric excess of *ca* 85% for **9**. Thus, there is a small amount of racemization during the steps leading from **17** to **19**, which most likely occurs during the hydrolysis of the oxazolidinone. The use of the more nucleophilic, less basic lithium hydroperoxide in this step[11] did not lead to any improvement.

The remaining steps of the synthesis required coupling of **9** with complex **8**. Conversion of **9** to the phenoxide by treatment with sodium hydride (0.98 equivalents to avoid the presence of excess base) in methylene chloride at 0 °C, followed by reaction with **8** in the presence of silver tetrafluoroborate,[14] afforded the diaryl ether

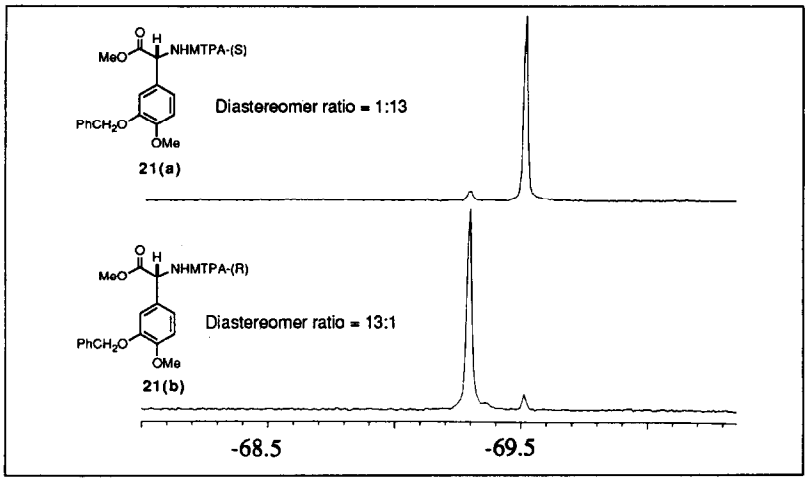


Figure 1. ^{19}F NMR Spectra of Compounds **21(a)** and **21(b)** (p.p.m. vs $CFCl_3$)

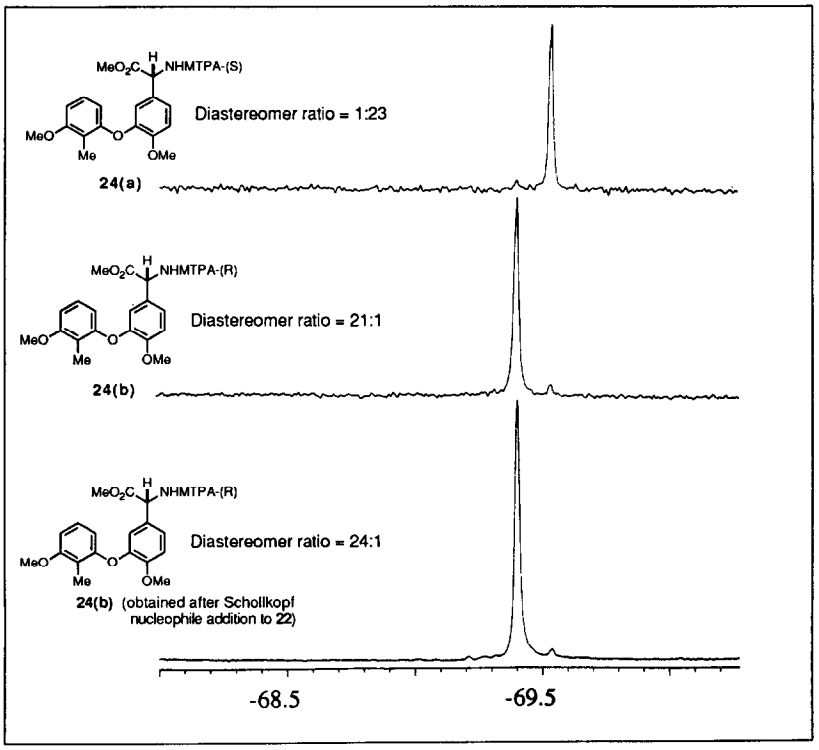
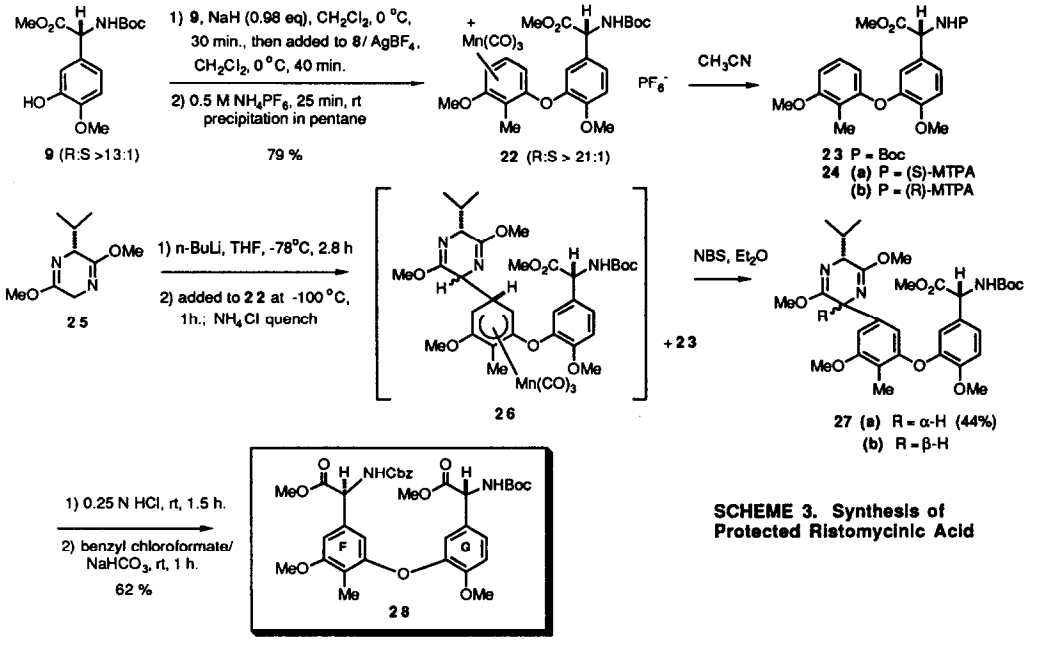


Figure 2. ^{19}F NMR Spectra of Compounds **24(a)** and **24(b)** (p.p.m. vs $CFCl_3$)

complex **22** (Scheme 3). The tetrafluoroborate of **22** was difficult to crystallize and, therefore, to purify, so it was converted to the hexafluorophosphate by treatment with aqueous NH_4PF_6. This gave a microcrystalline product in 79% yield from **9**. Since the arene-$Mn(CO)_3$ group in this complex is chiral (and racemic) a mixture of



SCHEME 3. Synthesis of Protected Ristomycinic Acid

diastereomers is produced, although these were indistinguishable in the ^1H NMR spectrum. In order to check for racemization during the coupling reaction, complex **22** was treated with acetonitrile to give the diaryl ether **23** and this was converted to the MTPA amides **24(a)** and **24(b)** by removal of the Boc group followed by coupling of the amino ester with (-) and (+)-MTPA, respectively. Inspection of the ^{19}F NMR spectra of the diastereomeric amides (Figure 2) reveals that the enantiomer ratio for **23** is *ca* 22:1. This is somewhat better than the enantiomeric excess recorded for **9**, and we tentatively attribute this to partial fractionation during the isolation of the hexafluorophosphate of **22**. The results are strongly indicative, however, that no racemization occurs during the aryl ether-forming step.

Introduction of the glycine side chain onto **22** was accomplished using Schöllkopf's chiral glycine enolate equivalent **25**.[15] During several early experiments we found that this coupling reaction was somewhat capricious, often giving very low yields of the desired product **26**. The main side reaction was decomplexation of **22** to give **23**, presumably by attack of the nucleophile at a carbonyl ligand, followed by disengagement of the arene with concomitant CO deinsertion, although we were never able to isolate stable manganese complexes that would prove this. Several approaches to solving this problem were examined, including the use alternative chiral glycine enolate equivalents,[16] as well as attempted deactivation of the arene-$Mn(CO)_3$ system by conversion to arene-

$Mn(CO)_2PR_3$ complexes,[17] were uniformly unsuccessful. Eventually, it was found that the protocol used for generating the lithiated bislactim was critical for the success of this reaction. Treatment of **25** with BuLi in THF at -78 °C *for 2.8 h prior to reaction with* **22** gave best results. The use of a shorter "aging" time led to greater amounts of decomplexation product, and longer times gave no further improvement. Reaction of the "aged" lithiobislactim with **22** for 1h at -100 °C, followed by cold quench with aqueous ammonium chloride, gave a mixture containing diastereomeric dienyl complexes **26** and arene **23**. This mixture was not separated or fully characterized, but was treated directly with N-bromosuccinimide (Et_2O, r.t., 20 min.) followed by $NaHSO_3$, to afford the diaryl ethers **27(a)** and **23** in 44% and 20% yields, respectively. Proton NMR spectroscopy on the crude product mixture indicated that minor amounts of the epimeric compound **27(b)** were also formed (approx. 4:1 ratio) but this was not isolated and separately characterized. Actually, the isolation of **23** from this reaction allowed us to test whether any racemization of the G-ring arylglycine occurs under the conditions for reaction of **22** with **25**. Conversion of recovered **23** to the (+)-MTPA amide **24(b)** as outlined earlier, followed by ^{19}F NMR spectroscopy indicated a diastereomer ratio of *ca* 25:1, virtually identical to that obtained after the initial formation of **22**, indicating that no racemization occurs under these reaction conditions.

Selective hydrolysis of the bislactim group of **27** was accomplished using 0.25 N HCl. No loss of Boc group was observed during this reaction, but the resulting amino ester was extremely difficult to handle. All attempts to isolate and purify this material led to several products, apparently resulting from dimerization and oligomerization (loss of methyl ester and formation of amides was noted in the NMR spectrum of crude material). Consequently, the ether extract from the hydrolysis reaction was treated directly with benzyl chloroformate to afford the fully protected ristomycinic acid derivative **28** in 62% yield from **27**.

In summary, we have shown that arene-manganese chemistry may be used to construct some rather complex and sensitive diarylglycine ethers, in a state of high optical purity, that are potentially valuable building blocks for the synthesis of ristocetin A. The observations regarding the quite sensitive nature of unprotected amino esters in this series are expected to be valuable in evaluating strategies for constructing the cyclic peptide framework that characterizes this group of natural products, and our future studies will be concerned with the development of approaches to the construction of such peptide linkages.

Experimental Section. For a general description of methods used for preparation, purification, handling and characterization of new compounds, see earlier publications from this laboratory.[7] Carbon-13 NMR spectra were recorded using a Varian Gemini 300 instrument, and the results of attached proton test (APT) are indicated by (+) or (-). All new compounds were judged to be at least 95% pure by ^1H and ^{13}C NMR spectroscopy.

Tricarbonyl(3-chloro-2-methylanisole)manganese tetrafluoroborate (8). To a stirred mixture of $Mn_2(CO)_{10}$ (394.4 mg, 1.0 mmol, 1.0 eq) and 3-chloro-2-methylanisole suspended in trifluoroacetic anhydride (20 mL) at 0 °C, was slowly added aqueous HBF_4 (48%, 3.9 mL, 29.5 mmol), and the mixture was stirred for 5 min. then refluxed for 16 h. After evaporation of the solvent *in vacuo*, the residue was dissolved in a mixture of dichloromethane (5 mL) and acetone (2 mL) and the product was precipitated with Et_2O (40 mL). After filtration the solid was washed with Et_2O (2 x 20 mL) and dried *in vacuo* to afford **8** (591.7 mg, 77 %) as a yellow solid.

Mp 133 °C (decompose); IR ($CHCl_3$) 2081, 2014 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 6.65 (t, J = 7.0, 1H), 6.23 (d, J = 7.0, 1H), 5.93 (d, J = 7.0, 1H), 3.91 (s, 3H), 2.31 (s, 3H).

1-Methylsulfinyl-1-methylthio-2-(3-benzyloxy-4-methoxyphenyl)ethylene (14). To a solution of the aldehyde **13** (4.99 g, 20.6 mmol., 1.0 eq) in 100 mL benzene, in a 250 mL flask equipped with Dean-Stark trap, was added methyl methylsulfinylmethyl sulfide (2.5 mL, 24.0 mmol, 1.2 eq) and Triton B (6.5 mL, 14.35 mmol, 0.7 eq) and the reaction mixture was refluxed for 45 min until no more water was collected. After cooling to room temperature, the mixture was acidified with 1 N HCl, diluted with 30 mL H_2O, shaken, extracted with CH_2Cl_2 (3 x 50 mL) and dried over $MgSO_4$. Evaporation of the solvent followed by purification by column chromatography (SiO_2, eluted with 1:1 hexanes/ethyl acetate) afforded the title compound (4.60 g, 64.3 %) as a colorless liquid which crystallized in the refrigerator: mp 82-84 °C; *Rf* 0.38 (3:1 hexanes/ethyl acetate); IR ($CHCl_3$) 3007, 1745, 1598, 1511, 1463, 1454, 1442, 1430 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.83 (d, *J* = 2.0 Hz, 1H), 7.49-7.27 (m, 7H); 5.23 (s, 2H, -OC*H*$_2$Ph); 3.95 (s, 3H, -SOC*H*$_3$); 2.09 (s, 3H, SC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9 (+, s); 147.7 (+, s); 136.9 (+, s); 136.8 (+, s); 136.10 (d, -); 128.5 (d, -); 127.8 (d, -); 127.0 (d, -); 126.3 (s, +); 125.1 (d, -); 114.1 (d, -); 111.1 (d, -); 70.7 (t, +, -O*C*H$_2$Ph); 55.9 (q, -, -O*C*H$_3$); 40.1 (q, -, -SO*C*H$_3$); 18.1 (q, -, -*C*H$_3$). HRMS: found (M^+-O) 332.0912, calcd for $C_{18}H_{20}S_2O_2$: 332.0905. MS: *m/e* 333 (9), 332 (35), 285 (100), 284 (17), 270 (33), 242 (8), 241(17).

2-(3-Benzyloxy-4-methoxyphenyl)acetic Acid (15). Into a solution of the sulfinyl derivative **14** (8.28 g, 23.8 mmol, 1.0 eq) in CH_2Cl_2 (160 mL) at -78 °C was bubbled HCl gas for 10 min. (which was generated by the addition of 16.5 mL of H_2SO_4 to 50 mL conc. HCl). EtOH (95 %, 12.6 mL, 1.2 eq) was added to the reaction mixture in one portion. After bubbling HCl for an additional 10 min. at -78 °C, the resulting dark brown solution was stirred at rt for 1h. To the mixture was slowly added 50 % KOH solution (24.5 mL, 604.1 mmol, 25 eq) followed by *ca* 100 mL EtOH as a co-solvent, and the reaction mixture was refluxed for 3 hrs after removal of CH_2Cl_2 using Dean-Stark apparatus. After cooling, the reaction mixture was extracted with EtOAc (4 x 250 mL) and the aqueous layer was acidified to pH = 2 with 1N HCl, extracted (CH_2Cl_2 , 4 x 250 mL), dried ($MgSO_4$), concentrated to afford a brownish yellow solid. Recrystallization from Et_2O afforded 4.0g of the title compound **15** as a white solid (60 %): mp 123-125 °C; *Rf* 0.47 (10:1 $CHCl_3$:MeOH); IR ($CHCl_3$) 3014, 1710, 1514, 1442, 1428, 1364 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H); 6.85 (s, 3H); 5.14 (s, 2H, -OC*H*$_2$Ph); 3.87 (s, 3H, -OC*H*$_3$); 3.55 (s, 2H, -C*H*$_2$CO$_2$H).

(4R,5S)-3-[2-(3-Benzyloxy-4-methoxyphenyl)-1-oxoethyl]-4-methyl-5-phenyl-2-oxazolidinone (16). To a stirred solution of the phenylacetic acid **15** (8.0 g, 29.4 mmol., 1.0 eq) in THF (300 mL) at -78 °C was added freshly distilled pivaloyl chloride (4.0 mL, 322.4 mmol, 1.1 eq) followed by Et_3N (5.3 mL, 380 mmol, 1.80 eq). The mixture was stirred for 15 min at -78 °C and 1h at rt to form the mixed anhydride and then cooled to -78 °C. In a separate flask 45 mL of a THF solution of (4R)-methyl-(5S)-phenyl-2-oxazolidinone was prepared and n-BuLi (2.5 M, 18.8 mL, 47.0 mmol, 1.60 eq) was added to the solution at -78 °C and stirred for 20 min. The mixture was then transferred to the mixed anhydride *via* cannula and stirred for 25 min. at -78 °C

and 20 h at rt. After quenching of the reaction with 0.5 M $KHSO_4$ (100 mL) and evaporation of volatiles *in vacuo*, the residue was extracted with dichloromethane (3 x 10 mL), dried ($MgSO_4$), filtered and concentrated. The resulting yellow oil was flash column chromatographed (SiO_2, hexanes:EtOAc = 5:1) and crystallized in Et_2O/hexanes mixture to afford the product (7.7g, 61 %) as a white solid. A second crop of the product (2.41g, 20 %) was obtained after repetition of the column chromatography on the liquors and crystallization. *Rf* 0.60 (1:2 hexanes:EtOAc); IR ($CHCl_3$) 3023, 3013, 1781, 1699, 1591, 1514, 1456, 1442, 1428, 1351, 1313 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.47-7.26 (m, 10H), 6.92-6.83 (m, 3H), 5.60 (d, *J* = 7.3 Hz, 1H), 5.15 (s, 2H, -CH_2Ph), 4.70 (dt, *J*=7.3, 6.6 Hz, 1H), 4.24 (d, *J* = 5.2 Hz, 1H), 4.15 (d, *J* =5.2 Hz, 1H), 3.87 (s, 3H, -OCH_3), 0.85 (d, J = 6.6 Hz,3H, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1 (s, +), 152.9 (s, +), 148.9 (s, +), 148.0 (s, +), 137.1 (s, +), 133.2 (s, +), 128.8 (d, -), 128.7 (d, -), 128.5 (d, -), 127.8 (d, -), 127.4 (d, -), 125.9 (s, +), 125.6 (d, -), 122.5 (d, -), 115.3 (d, -), 111.8 (d, -), 78.9 (d, -), 70.9 (t, +), 56.0 (q, -), 55.0 (d, -), 41.1 (t, +), 14.4 (q, -); $[\alpha]_D$ + 5.2° (c 2.33, $CHCl_3$); HRMS: found (M^+) 431.1724; calcd for $C_{26}H_{25}NO_5$: 431.1733. MS: *m/e* 431 (17), 332 (20), 267 (17), 243 (21), 239(14), 221 (25), 218 (18), 217 (16).

[3(2R),4R,5S]-3-[2-azido-2(3-benzyloxy-4-methoxyphenyl)-1-oxoethyl]-4-methyl-5-phenyl-2-oxazolidinone (17). To a stirred solution of imide **16** (1.01 g, 2.32 mmol, 1.0 eq) in THF (50 mL) at -78 °C was added 0.5 M potassium bistrimethylsilylamide (4.86 mL, 2.43 mmol, 1.05 eq) via cannula and the mixture was stirred for 23 min. at -78 °C to form the enolate. In a separate flask at -78 °C, a solution of trisylazide (896 mg, 2.90 mmol, 1.25 eq) in THF (13 mL) was prepared and was transferred to the enolate solution *via* cannula. After 2 min. stirring at -78 °C, the reaction was rapidly quenched by 170 μL of glacial acetic acid and heated up to rt in a 55 °C water bath. After 3 h stirring, the reaction mixture was partitioned between brine (100 mL) and Et_2O (150 mL), shaken and separated. The aqueous layer was extracted with Et_2O (3x100 mL) and the combined organic layer was dried over Na_2SO_4. Concentration and purification (SiO_2, hexanes:EtOAc = 5:1) afforded the product as a yellow oil (90 % yield, 92 % d.e.). Crystallization from Et_2O afforded the single diastereomer (71 %) as a white solid. Mp 116-118 °C; *Rf* 0.36 (3:1 hexanes:EtOAc); IR ($CHCl_3$) 2110 (-N_3), 1783, 1708, 1515, 1368 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48-7.23 (m, 10H), 7.04 (d, *J* = 8.3 Hz, 1H), 7.02 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.11 (s, 1H), 5.39 (d, *J* = 7.1 Hz, 1H), 5.18 (dd, *J* = 18.4, 12.5 Hz, 2 H, -CH_2Ph), 4.56 (dt, *J* = 7.1, 6.4 Hz, 1H), 3.90 (s, 3H, -OCH_3), 0.96 (d, *J* = 6.4 Hz, 3H, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.10 (s, +), 151.94 (s, +), 150.62 (s, +), 148.22 (s, +), 136.81 (s, +), 132.60 (s, +), 128.92 (d, -), 128.77 (d, -), 128.54 (d, -), 127.83 (d, -), 127.49 (d, -), 125.50 (d, -), 125.05 (s, +), 122.20 (d, -), 113.53 (d, -), 111.82 (d, -), 79.19 (d, -, -CHN_3), 70.85 (t, +, -OCH_2Ph), 63.61 (d, -), 55.97 (q, +), 55.42 d, -), 14.43 (q, +); $[\alpha]_D$ -130.6° (c 1.85, $CHCl_3$); HRMS: found 444.1678; calcd for $C_{26}H_{24}N_2O_5$: (M^+-N_2) 444.1685. MS: *m/e* 444, 338, 309, 295, 281, 254, 247.

Methyl (2R)-azido-2-(3-benzyloxy-4-methoxyphenyl)acetate (19). To a solution of azidoimidate **17** (731.5 mg, 1.55 mmol, 1.0 eq) in THF:H_2O (3:1, 36 mL), cooled in an ice bath, was added LiOH·H_2O (122.9 mg, 2.93 mmol, 1.89 eq) and the mixture was stirred for 35 min. until the starting material had disappeared (TLC). After evaporation of volatiles *in vacuo*, the residue was acidified to pH = 1 with 1 N HCl,

extracted with CH_2Cl_2 (3 x 20 mL) and dried ($MgSO_4$). After evaporation of solvent the crude product was dissolved in MeOH (4 mL) containing *p*-toluenesulfonic acid (588.7 mg, 3.09 mmol, 2.0 eq), and the solution was refluxed for 5 h until all the starting material had disappeared (TLC). After cooling, brine (5 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the crude product by column chromatography (SiO_2, eluted with 5:1 ethyl acetate/hexanes) afforded **19** (467.4 mg, 92.2 %) as a colorless liquid. *Rf* 0.69 (2:3 hexanes:EtOAc); IR ($CHCl_3$) 3031, 2109, 1747, 1604, 1593, 1515, 1464, 1456, 1442, 1429 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.43-7.34 (m, 5H), 6.93-6.92 (m, 3H), 5.16 (s, 2H, -CH_2Ph), 4.86 (s, 1H, N_3CH), 3.90 (s, 3H, -OCH_3), 3.71 (s, 3H, -CO_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6 (s, +), 150.5 (s, +), 148.4 (s, +), 136.6 (s, +), 128.5 (d, -), 127.9 (d, -), 127.4 (d, -), 125.9 (s, +), 121 (d, -), 113.0 (d, -), 111.7 (d, -), 71.0 (t, +, CH_2Ph), 65.0 (d, -, -N_3CH), 56.0 (q, -, OCH_3), 52.8 (q, -, CO_2CH_3) ; $[\alpha]_D$ -110.6° (c 2.84, $CHCl_3$); HRMS: found (M^+) 327.1216; calcd for $C_{17}H_{17}N_3O_4$ 327.1219. MS: *m/e* 328 (7), 327 (26.8), 299 (10), 285 (11), 266 (10), 241 (15), 240 (22), 239 (24), 208 (22).

Procedure for the Conversion of 19 into 21(a) and 21(b). The azidoester **19** (15.7 mg, 0.048 mmol) was stirred in THF (1.5 mL) with triphenylphosphine (18.9 mg, 1.5 equiv.) for 15 h at rt until all starting material was consumed according to TLC. Water (18 μL, 21 equiv.) was added and the mixture was stirred for 42 h. After evaporation of volatiles, purification by TLC (SiO_2, EtOAc) afforded the amino ester **20** (7.9 mg, 55%). The product (2.9 mg) was dissolved in methylene chloride (2.5 mL) and treated with HOBT (2.8 mg, 2.5 equiv.) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.8 mg, 1.8 equiv.) followed by (-)-MTPA (3.8 mg, 2.0 equiv.) and the mixture was stirred for several hours at rt under N_2 atmosphere. Volatiles were evaporated in vacuo and the diastereomer ratio was estimated by ^{19}F NMR spectroscopy (Fig. 1) of the product **21(a).** An identical procedure employing (+)-MTPA was used to prepare **21(b).** Further purification by TLC did not lead to significant fractionation of diastereomers.

Methyl (2R)-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-(3-hydroxy-4-methoxyphenyl)acetate (9). A solution of di-*tert*-butyl dicarbonate (281.3 mg, 1.29 mmol, 1.24 eq) in EtOAc (5.5 mL) was combined with 10 % palladium on activated carbon (104.7 mg) and through the mixture was bubbled H_2 for 2 h 20 min. for presaturation. The azido methyl ester **19** (347.7 mg, 1.06 mmol, 1.0 eq) was added to the solution and stirring was continued for 24 h while bubbling the H_2 until all starting material had disappeared (TLC). After filtration over Celite, the solution was concentrated and the product was purified by column chromatography (SiO_2, eluted with 3:1 ethyl acetate/hexanes) to afford **9** (311.6 mg, 94.2 %) as a pale yellow liquid which solidified in the refrigerator. Mp 113.5-114.5 °C; *Rf* 0.70 (1:1 hexanes:EtOAc); IR ($CHCl_3$) 3543, 3439, 3029, 1742, 1711, 1596, 1510, 1497, 1458, 1438, 1393, 1368, 1331 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.93-6.79 (m, 3H), 5.66 (s, 1H, -O*H*), 5.51 (bs, 1H, -N*H*Boc), 5.23 (bd, J = 6.4 Hz, 1H, BocNHC*H*), 3.88 (s, 3H , -OCH_3), 3.72 (s, 3H, -CO_2CH_3), 1.43 (s, 9 H, -CMe_3 ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8 (s, +), 146.6 (s, +), 145.9 (s, +), 130.0 (s, +), 119.1 (s, +), 118.9 (d, -), 113.2 (d, -), 110.7 (d, -), 80.1 (s, +), 57.1 (d, -), 55.9 (q, -), 52.6 (q, -), 28.3 (q, -); $[\alpha]_D$ -126.5° (c 1.25, $CHCl_3$); HRMS: found (M^+) 311.1352, calcd for $C_{15}H_{21}NO_6$: 311.1369. MS: *m/e* 311 (1), 255 (4), 223 (9), 197 (3), 196 (18).

3-[(Tricarbonyl)(η^6 2-methyl-3-methoxyphenyloxy)manganese][N-t-butoxycarbonyl-(R)-4-methoxyphenylglycine methyl ester] hexafluorophosphate (22). To a stirred suspension of 60 % NaH (11.6 mg, 0.29 mmol, 0.98 eq) in dichloromethane (2.5 mL) at 0 °C was added *via* cannula an ice cold solution of the phenol **9** (92.2 mg, 0.30 mmol, 1.0 eq) in dichloromethane (3 mL). The mixture was stirred for 30 min. at 0 °C and the resulting yellow solution was then transferred to a mixture of arene-manganese complex **8** (125.6 mg, 0.33 mmol, 1.10 eq) and $AgBF_4$ (307.3 mg, 2.8 mmol, 9.5 eq) suspended in dichloromethane (23 mL) at 0 °C. After 40 min. stirring at 0 °C, the reaction was quenched by addition of 0.5 M NH_4PF_6 solution (15 mL) and the mixture was vigorously stirred for 25 min., separated, and extracted with dichloromethane (2 x 15 mL). The combined organic layer was washed with 0.5 M NH_4PF_6 (2 x 15 mL) and dried over Na_2SO_4. After filtration, the solution was concentrated to 1~2 mL and the product was precipitated with ~ 60 mL pentane, filtered, and washed (pentane, 30 mL) to afford the complex **22** (166.5 mg, 79 %) as a yellow solid. IR ($CHCl_3$) 3023, 2071, 2003, 1744, 1712, 1534, 1512, 1496, 1472, 1428 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39 (d, J = 8.6 Hz, 1H), 7.26 (s, 1H), 7.10 (d, J = 8.6 Hz, 1H), 6.68 (t, J = 7.3 Hz, 1H), 6.08 (d, J = 7.0 Hz, 1H), 5.71 (bs, 1H), 5.43 (d, J = 7.0Hz, 1H), 5.29 (bd, J = 6.9 Hz, 1H), 4.15 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H), 2.40 (s, 3H), 1.43 (s, 9H). Anal. calcd: C 43.65, H 4.09, N 1.96. Found: C 43.31, H 4.31, N 1.85 %.

3-{2-Methyl-3-methoxy-5-[(4R)-isopropyl-3,6-dimethoxypyrazinyl]phenyloxy}[N-t-Butoxycarbonyl-(R)-4-methoxyphenylglycine methyl ester] (27a). To a solution of (6R)-isopropyl-2,5-dimethoxypyrazine (**25**) (15.7 mg, 0.085 mmol, 2.0 eq) dissolved in THF (850 µL) at -78 °C was added dropwise n-BuLi (32 µL, 2.71 M, 2.0 eq), and the mixture was stirred for 2 h 45 min. at -78 °C. This reaction mixture was quickly added to the diarene-Mn complex **22** (30.0 mg , 0.042 mmol, 1.0 eq) at -100 °C. The reaction mixture was then stirred for 1 h between -95 and -100 °C (liq. N_2/ pentane bath) and the reaction was quenched with sat. NH_4Cl (1.5 mL) at -100 °C. After warming, the mixture was extracted with Et_2O (3x5 mL) and the combined organic layer was washed with brine (5 mL) and dried (Na_2SO_4). After filtration, N-bromosuccinimide (7.8 mg, 0.044 mmol, 1.04 eq) was added and the mixture was stirred for 20 min at rt. The reaction was quenched with 3 mL of sat. sodium bisulfite and the mixture was extracted with Et_2O (3x5 mL), washed with brine (1 x 5 mL), dried ($MgSO_4$) and concentrated to afford a yellow oil. Purification by preparative TLC (SiO_2, hexanes:EtOAc=3.5:1, 6 times developed) afforded compound **27a** (11.4 mg, 44.3 %) as a white solid along with the demetallation side product **23** (3.7 mg, 20 %) as a colorless oil. Compound **27a**: mp 60-62 °C; R_f 0.50 (2:1 hexanes:EtOAc); IR ($CHCl_3$) 3025, 3015, 2972, 1745, 1696, 1512, 1494, 1464, 1437, 1418 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.04 (d, J = 8.3 Hz, 1H), 6.93, (d, J = 8.4 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 6.56 (s, 1H), 6.34 (s, 1H), 5.37 (bs, 1H), 5.14 (bd, 1H, -HN$CH$$CO_2$Me), 4.96 (d, J = 3.5 Hz, 1H), 4.00 (t, J = 3.5 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.68 (s, 3H), 3.62 (s, 3H), 2.33 (m, 1H), 2.07 (s, 3H, PhCH_3), 1.41 (s, 9H), 1.07 (d, J = 6.90 Hz, 3H), 0.72 (d, J = 6.83 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6 (s, +), 162.3 (s, +), 158.7 (s, +), 154.7 (s, +), 150.3 (s, +), 146.6 (s, +), 138.9 (s, +), 129.3 (s, +), 121.9 (d, -), 116.9 (s, +), 116.8 (d, -), 112.6 (d, -), 110.7 (d, -), 105.6 (d, -), 80.1 (s, +), 60.6 (d, -), 59.8 (d, -), 57.0 (d, -), 56.1 (q, -), 55.7 (q, -), 53.0 (q, -), 52.5 (q, -), 31.6 (d, -), 28.3 (q, -), 19.1 (q, -), 16.5 (q, -),

8.8 (q, -); $[\alpha]_D$ +1.67° (c 0.78, $CHCl_3$); HRMS: found (M^+): 613.2994; calcd for $C_{32}H_{43}N_3O_9$ 613.2999. MS: *m/e* 614 (3), 613 (26), 513 (13), 498 (20), 488 (20), 455 (28), 454 (100), 452 (19).

3-(2-Methyl-3-methoxyphenyloxy)[*N*-*t*-Butoxycarbonyl-(R)-4-methoxyphenylglycine] methyl ester (23). This compound was isolated from the reaction of **22** with **25**, and was also prepared by decomplexation of **22** using acetonitrile as previously described.[7] *Rf* 0.58 (2:1 hexanes:EtOAc); IR ($CHCl_3$) 1712, 1583, 1512, 1496, 1470, 1438, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.04 (t, *J* = 8.1 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 2.1 Hz, 1H), 6.62 (d, *J* = 8.2, 0.6 Hz, 1H), 5.40 (bs, 1H), 5.13 (bd, 1H), 3.84 (s, 6H, -OC*H*$_3$), 3.65 (s, 3H, -CO_2CH_3), 2.11 (s, 3H, -C*H*$_3$), 1.38 (s, 9H, -(C*H*$_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 155.3, 150.5, 146.6, 129.5, 126.4, 122.1, 117.3, 112.7, 110.8, 105.7, 80.1, 56.9, 56.1, 55.7, 52.4, 28.1, 8.8 ; $[\alpha]_D$ - 93.8° (c 0.42, $CHCl_3$); HRMS. Found: 431.1937; calc'd for $C_{23}H_{29}NO_7$: 431.1944. MS: m/e 431(2), 376(4), 358(4), 357(8), 342(5), 331(3), 330(8), 214(32). For the assessment of optical purity of complex **22**, the following procedure was followed for the preparation of the MTPA derivatives **24**. The N-Boc protected diarylamine-manganese complex **22** (10 mg) was stirred overnight in CH_3CN (1.5 mL). The resulting brown sludge was filtered over Celite and the crude product was purified by TLC in the usual way (hexanes:EtOAc = 2:1) to afford the protected diaryl ether (5.9 mg, 98 %) as a colorless oil. This compound (2.9 mg, $7.0x10^{-6}$ mol, 1.0 eq) dissolved in MeOH (250 μL) was combined with 6N HCl (250 μL) and stirred for 45 min. until all the starting material disappeared. Volatiles were pumped out *in vacuo* for an hour, residual water was removed by co-evaporation with benzene (1.5 mL x 2) and the residue was dried *in vacuo* for 1h. The resulting amino acid salt was combined with HOBT (2.9 mg, 2.5 eq) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.9 mg, 2.2 eq) followed by (+)-MTPA (3.4 mg, 2.1 eq) dissolved in CH_2Cl_2 (2 mL) and the mixture was stirred for 2.8 h under N_2 atmosphere until all the starting material was consumed (TLC, NMR). Volatiles were evaporated *in vacuo* and the diastereomeric ratio was determined by ^{19}F-NMR. (Fig. 2).

[*N*-*t*-Butoxycarbonyl-(R)-3-hydroxy-4-methoxyphenylglycine methyl ester]-O-[N-benzyl oxycarbonyl-(S)-2-methyl-3-methoxyphenylglycine methyl ester] (28). The bislactim adduct **27** (13.8 mg) was dissolved in THF (1.2 mL), combined with 0.25 N HCl (270 μL) and was stirred for 1.5 h at rt until all the starting material was consumed (TLC). After evaporation of the volatiles *in vacuo*, the residue was partitioned between Et_2O (1 mL) and sat. $NaHCO_3$ solution (1 mL), and benzyl chloroformate (6.5 μL) was added to the solution. After 1 h 10 min. stirring, the mixture was extracted with Et_2O (3 x 3 mL), dried (Na_2SO_4), and the solvent was removed *in vacuo*. Purification by preparative TLC (SiO_2, hexanes:EtOAc = 4:3) afforded the protected ristomycinic acid **28** (8.9 mg, 62.1 %) as a colorless oil. *Rf* 0.41 (2:1 hexanes:EtOAc); IR ($CHCl_3$) 3436, 3007, 2955, 1743, 1714, 1582, 1492, 1450, 1439, 1420 cm^{-1}; ^1H NMR (300 MHz, 58 °C, $CDCl_3$ + 1 drop C_6D_6) δ 7.30 (s, 5H), 7.05 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.76 (s, 1H), 6.61 (s, 1H), 6.39 (s, 1H), 5.64 (br. s, 1H), 5.37 (br. s, 1H), 5.19 (br. s, 1H), 5.13 (br. s, 1H), 5.08 (br. s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.67 (s, 3H), 3.66 (s, 3H), 2.12 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 (s, +), 171.2 (s, +), 159.1 (s, +), 155.4 (s, +), 154.8 (s, +), 150.5 (s, +), 146.1 (s, +), 136.1

(s, +), 134.9 (s, +), 129.4 (d, -), 128.5 (d, -), 128.2 (d, -), 122.7 (d, -), 118.1 (s, +), 117.4 (d, -), 112.8 (d, -), 109.5 (d, -), 104.6 (d, -), 80.1 (s, +), 67.1 (t, +), 57.9 (d, -), 56.9 (d, -), 56.1 (q, -), 55.8 (q, -), 52.8 (q, -), 52.6 (q, -), 28.3 (q, -), 8.8 (q, -). $[\alpha]_D$ - 4.2° (c = 0.66 , $CHCl_3$). HRMS. Found: 551.2028; calcd for $C_{29}H_{31}N_2O_9$ (M^+-Boc): 551.2029. A molecular ion could not be obtained for this compound. *m/e* 593(1), 578(2), 553(3), 552(5), 551(3), 496 (4), 495(18), 494(53).

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