Asymmetric Sharpless Dihydroxylation Reaction of Chiral Bishomoallylic Alcohols: Application to the Synthesis of the C1–C10–C5 Fragment of FR225654

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Abstract: Toward the synthesis of FR225654, an antidiabetic natural product, the Sharpless asymmetric dihydroxylation of chiral bishomoallylic alcohols, never reported in the literature, was examined. Employing the pyrimidine class of ligands, a high level of matched diastereoselectivity was obtained. An application to the stereoselective synthesis of the C1–C10–C5 fragment of FR225654 was performed.

Key words: stereoselective synthesis, natural products, dihydroxylation, diols, diastereoselectivity

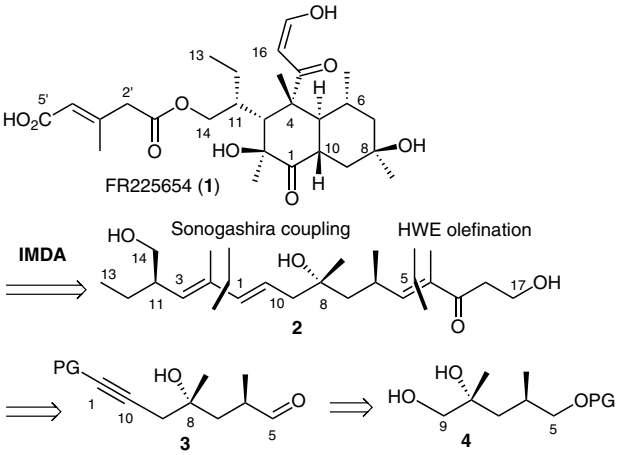
As part of a screening program searching for new antidiabetic agents, FR225654 (**1**) was isolated from the culture broth of *Phoma* sp. no. 00144.[1] This *trans*-decalone selectively inhibited gluconeogenesis of rat primary hepatocytes and had significant hypoglycemic effects in several in vivo mouse models.

We have been interested in developing a synthesis of this natural product from triene **2** by means of an intramolecular Diels–Alder reaction (Scheme 1). Triol **4** was chosen as the starting material for the synthesis of the central part C1–C10–C5 (**3**).

It is interesting to note that this structural motif, 2,4-dimethylpentane-1,2,5-triol (**4**), is often found in biologically active natural products (macrolide antibiotics, etc.) and synthetic intermediates of organic substances (Figure 1).[2]

We envisioned to develop a general and efficient stereoselective method for synthesizing this unit by means of Sharpless asymmetric dihydroxylation (SAD)[3] of the corresponding chiral bishomoallylic alcohol **5** (Scheme 2).[4,5]

In the context of a substrate-directed dihydroxylation reaction, prior interesting works have been reported.[6] However, to our knowledge, no publication reports the SAD reactions of such chiral olefins. In this context, Corey has evidenced that the combined use of the *p*-methoxybenzoate protecting group and the noncommercial



Scheme 1 Retrosynthetic analysis of FR225654 (**1**)

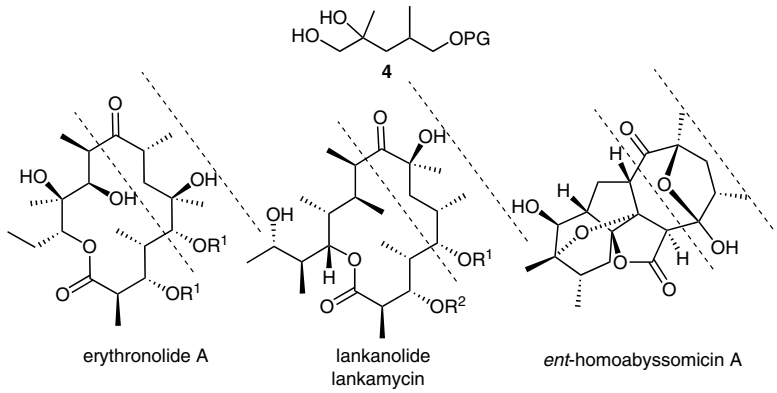


Figure 1 Biologically active natural products including structural motif **4**

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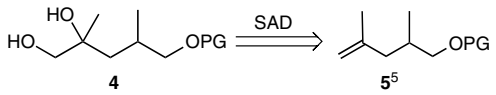
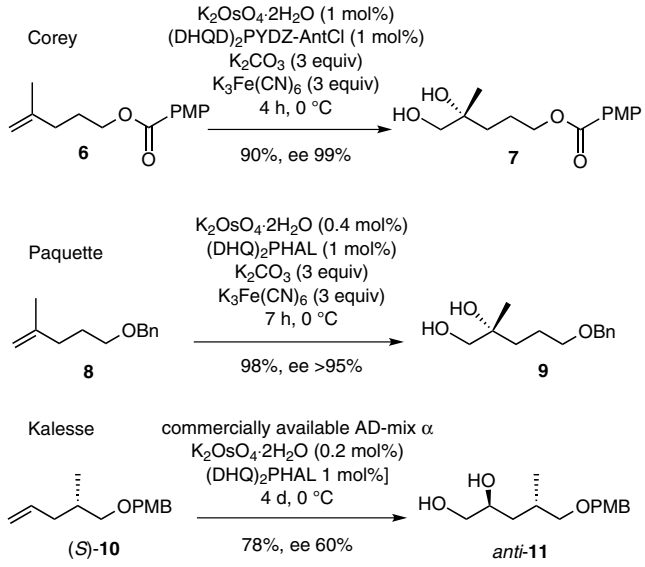


Scheme 2 Synthesis of chiral bishomoallylic alcohol **4** by means of the SAD reaction of olefin **5**

$(DHQD)_2PYDZ$-AntCl ligand permit to reach high enantiomeric excesses in the SAD of achiral bishomoallylic alcohols by enhancing aryl–aryl contacts.[7] Hence, synthesis of diol **7** was achieved in high yield and enantiomeric excess from olefin **6** (Scheme 3). More surprisingly, Paquette reported the dihydroxylation of achiral benzyl ether **8** derived from 4-methylpent-4-en-1-ol using commercial $(DHQ)_2PHAL$ as ligand to access diol **9** in high yield and selectivity.[8a,b] In contrast, results are markedly lower for chiral substrates in double diastereoselection. In 2008, Kalesse described the SAD reaction of the PMB ether of (*S*)-2-methyl-4-pentenol (*S*)-**10** with commercial AD-mix-α to provide diol *anti*-**11**. The reaction sluggishly proceeded within three days and delivered the diol in a poor 4:1 diastereomeric ratio.[9]

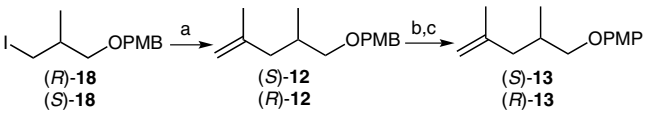


Scheme 3 Synthesis of diols **7**, **9**, and *anti*-**11** by the SAD reaction

We describe here the results of our study to optimize the SAD reaction of chiral olefin **5** with the aim of a stereoselective preparation of triol **4**. The experiments were performed to assess the relative ability of different ligands in the context of matching and mismatching.

As this study has been carried out in the context of total synthesis, the choice of the alcohol protecting group is critical and unfortunately, *p*-methoxybenzoate and benzyl groups were unsuitable. PMB and PMP groups, on the other hand, gave satisfactory results. For this purpose, we examined the reactivity of olefins (*R*)- and (*S*)-**12** (OPMB) and (*R*)- and (*S*)-**13** (OPMP) using $(DHQ)_2$ or $(DHQD)_2$ ligands and PHAL, AQN, or PYR as linkers. Reactions were performed under stronger conditions (i.e. 1 mol% $K_2OsO_4 \cdot 2H_2O$) in order to selectively access triols **14**–**17** and *ent*-**14**–**17** (Scheme 4).[10] The data for these experiments are summarized in Tables 1 and 2.

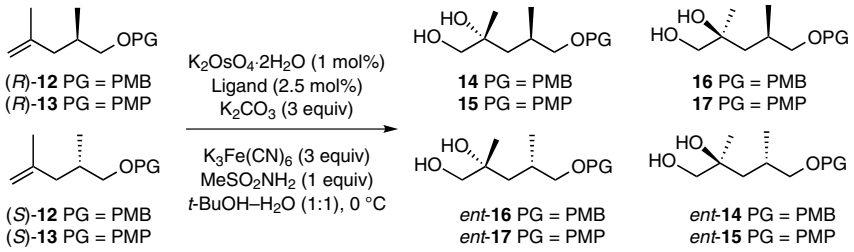
The synthesis of SAD precursors (*R*)- and (*S*)-**12** (OPMB) was accomplished, respectively, from known (*S*)- and (*R*)-iodides **18**[11] through a Cu(I)-catalyzed cross-coupling reaction with 2-propenylmagnesium bromide.[12] Cleavage of the PMB ether and subsequent protection of the hydroxyl function as its PMP ether provided the corresponding (*R*)- and (*S*)-**13** olefins (Scheme 5).[13,14]



Scheme 5 Synthesis of olefins **12** and **13**. *Reagents and conditions*: (a) CuI, H_2C=C(Me)-MgBr, THF, –78 °C to r.t., 14 h, 95%; (b) DDQ, CH_2Cl_2–H_2O (20:1), 0 °C to r.t., 12 h, 72%; (c) Ph_3P, PMPOH, DIAD, CH_2Cl_2, 0 °C to r.t., 3 h, 98%.

We initiated our investigation by carrying out the osmylation of (*R*)- and (*S*)-**12** in the absence of chiral ligands (Table 1, entries 1 and 8);[14] however, these reactions only displayed a low diastereoselectivity. The SAD reaction of (*R*)- and (*S*)-**12** was then studied (Table 1, entries 2–7 and 9–14). It was found that pyrimidine derivatives $(DHQD)_2PYR$ or $(DHQ)_2PYR$ were the ligands of choice in matched reactions to afford **14** or *ent*-**14** with high yield and stereoselectivity (dr = 96:4 and 91:9; Table 1, entries 6 and 14).

However, in mismatched reactions, very low diastereoselection was observed to provide **16** or *ent*-**16**, regardless the ligand, that is, $(DHQ)_2$ or $(DHQD)_2$ and the linker (PHAL, AQN, or PYR) (Table 1, entries 3, 5, 7, 9, 11 and 13): in all cases, it appears that overriding the intrinsic diastereofacial preference of the olefin substrate is difficult for the dihydroxylation reagent.



Scheme 4 Synthesis of triols **14**–**17** and *ent*-**14**–**17**

Table 1 SAD of Olefins (*R*)-**12** and (*S*)-**12** (OPMB)

Entry	Substrate	Ligand (2.5 mol%)	Yield (%)[a]	Time (h)	dr[b]
1	(*R*)-**12**	–	quant.	12	**14**/**16** 57:43
2	(*R*)-**12**	$(DHQD)_2$-PHAL	quant.	4	**14**/**16** 54:46
3	(*R*)-**12**	$(DHQ)_2$-PHAL	quant.	12	**14**/**16** 23:73
4	(*R*)-**12**	$(DHQD)_2$-AQN	quant.	12	**14**/**16** 73:27
5	(*R*)-**12**	$(DHQ)_2$-AQN	quant.	12	**14**/**16** 43:57
6	(*R*)-**12**	$(DHQD)_2$-PYR	quant.	12	**14**/**16** 96:4
7	(*R*)-**12**	$(DHQ)_2$-PYR	quant.	12	**14**/**16** 33:67
8	(*S*)-**12**	–	quant.	12	*ent*-**14**/*ent*-**16** 57:43
9	(*S*)-**12**	$(DHQD)_2$-PHAL	quant.	3	*ent*-**14**/*ent*-**16** 45:55
10	(*S*)-**12**	$(DHQ)_2$-PHAL	quant.	3	*ent*-**14**/*ent*-**16** 59:41
11	(*S*)-**12**	$(DHQD)_2$-AQN	quant.	12	*ent*-**14**/*ent*-**16** 39:61
12	(*S*)-**12**	$(DHQ)_2$-AQN	quant.	12	*ent*-**14**/*ent*-**16** 73:23
13	(*S*)-**12**	$(DHQD)_2$-PYR	quant.	2	*ent*-**14**/*ent*-**16** 35:65
14	(*S*)-**12**	$(DHQ)_2$-PYR	quant.	12	*ent*-**14**/*ent*-**16** 91:9

[a] Isolated yield.
[b] Determined by HPLC.

Considering observations made by Corey,[7] a variation of the alcohol protecting group from PMB to PMP was envisioned in order to modify the catalyst–substrate interaction while keeping favorable π-interactions, SAD experiments were thus performed on the corresponding OPMP ethers (*R*)- and (*S*)-**13** to yield **15** or **17** and *ent*-**15** or *ent*-**17**.

Similar results were observed in the context of matched and mismatched pairing (Table 2, entries 2–7 and 9–14); however, it is interesting to note a remarkable increase of

Table 2 SAD of Olefins (*R*)-**13** and (*S*)-**13** (OPMP)

Entry	Substrate	Ligand (2.5 mol%)	Yield (%)[a]	Time (h)	dr[b]
1	(*R*)-**13**	–	quant.	12	**15**/**17** 55:45
2	(*R*)-**13**	$(DHQD)_2$-PHAL	quant.	3.5	**15**/**17** 55:45
3	(*R*)-**13**	$(DHQ)_2$-PHAL	quant.	3.5	**15**/**17** 41:59
4	(*R*)-**13**	$(DHQD)_2$-AQN	quant.	3.5	**15**/**17** 72:28
5	(*R*)-**13**	$(DHQ)_2$-AQN	quant.	3.5	**15**/**17** 34:66
6	(*R*)-**13**	$(DHQD)_2$-PYR	quant.	1.5	**15**/**17** 92:8
7	(*R*)-**13**	$(DHQ)_2$-PYR	quant.	1.5	**15**/**17** 37:63
8	(*S*)-**13**	–	quant.	12	*ent*-**15**/*ent*-**17** 58:42
9	(*S*)-**13**	$(DHQD)_2$-PHAL	quant.	3	*ent*-**15**/*ent*-**17** 45:55
10	(*S*)-**13**	$(DHQ)_2$-PHAL	quant.	3	*ent*-**15**/*ent*-**17** 62:38
11	(*S*)-**13**	$(DHQD)_2$-AQN	quant.	3	*ent*-**15**/*ent*-**17** 34:66
12	(*S*)-**13**	$(DHQ)_2$-AQN	quant.	3	*ent*-**15**/*ent*-**17** 74:26
13	(*S*)-**13**	$(DHQD)_2$-PYR	quant.	2	*ent*-**15**/*ent*-**17** 36:64
14	(*S*)-**13**	$(DHQ)_2$-PYR	quant.	2	*ent*-**15**/*ent*-**17** 89:11

[a] Isolated yield.
[b] Determined by HPLC.

Table 3 SAD of (*S*)-**10** and (*R*)-**10** and Olefin **19**

Entry	Substrate	Ligand (2.5 mol%)	Yield (%)[a]	Time (h)	dr[b]
1	(*S*)-**10**	$(DHQ)_2$-PHAL	90	3	*anti*-**11**/*syn*-**11** 81:19
2	(*S*)-**10**	$(DHQ)_2$-PYR	87	5	*anti*-**11**/*syn*-**11** 91:9
3	(*R*)-**10**	$(DHQD)_2$-PYR	80	7	*anti*-*ent*-**11**/*syn*-*ent*-**11** 96:4
4	(*R*)-**19**	–	quant.	12	*anti*-**20**/*syn*-**20** 52:48
5	(*R*)-**19**	$(DHQD)_2$-PYR	quant.	5	*anti*-**20**/*syn*-**20** 90:10

[a] Isolated yield.
[b] Determined by HPLC.

the turnover rate. These conditions have also proven to be very useful for the SAD of Kalesse olefins (*S*)-**10** and (*R*)-**10** (Table 3).[9] Ratio preferences of 91:9 and 96:4 were observed in the reaction employing PYR as linker to yield **11** and *ent*-**11** both *anti* (Table 3, entries 2 and 3).

A similar set of experiments was carried out on olefin (*R*)-**19** to yield diol **20** in high selectivity in a matched pair (Scheme 6, Table 3, entries 4 and 5).

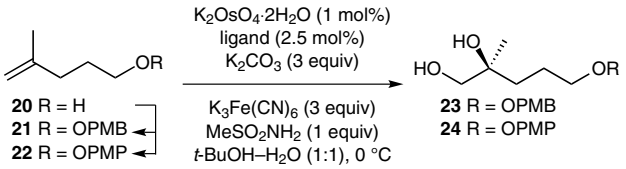
As a final point, SAD reaction of achiral Paquette olefin **8** (OBn) was re-examined. However, in our hands, under previously reported conditions,[8a] enantiocontrol was only 58% ee (Table 4, entry 1).

Table 4 SAD of Olefins **8**, **21**, and **22**

Entry	Substrate	Ligand	Yield (%)[a]	Time (h)	er[b]
1	**8**	$(DHQ)_2$-PHAL	quant.	4[8a]	**9** 79:21
2	**21**	$(DHQD)_2$-PHAL	quant.	1	**23** 83:17
3	**21**	$(DHQD)_2$-AQN	quant.	2	**23** 87:13
4	**21**	$(DHQD)_2$-PYR	quant.	2	**23** 85:15
5	**22**	$(DHQD)_2$-PHAL	quant.	1	**24** 84:16
6	**22**	$(DHQD)_2$-AQN	quant.	2	**24** 92:8
7	**22**	$(DHQD)_2$-PYR	quant.	1	**24** 85:15

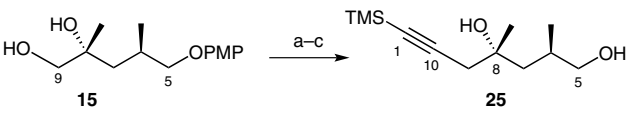
[a] Isolated yield.
[b] Determined by HPLC.

Based on our work, SAD reaction of achiral olefins **21** (OPMB) and **22** (OPMP) was then examined under stronger conditions. Surprisingly, slightly better results were obtained with AQN rather than with PYR spacer; however, the enantiomeric excess of diols **23** and **24** could not exceed 74% and 84% (Table 4, entries 3 and 6). Noteworthy, both starting materials **21** (OPMB) and **22** (OPMP) were easily obtained from alcohol **20** (Scheme 7).



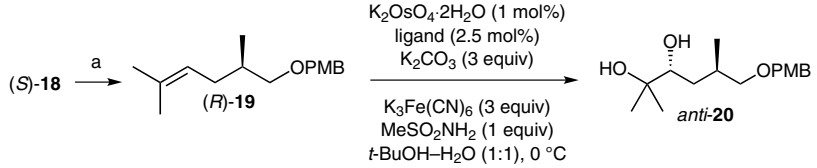
Scheme 7 Synthesis of diols **23** and **24**

Finally, the SAD product **15** was easily transformed into the desired fragment C1–C10–C5 (**25**) of FR225654, after epoxidation, epoxide ring opening with trimethylsilylacetylide, and deprotection (Scheme 8).[15]



Scheme 8 Synthesis of fragment **25**. *Reagents and conditions*: (a) MsCl, LDA, THF, –10 °C, 3 h; (b) *n*-BuLi, $BF_3{\cdot}OEt_2$, $HCCSiMe_3$, THF, –78 °C to r.t., 3 h, 70% (2 steps); (c) CAN, $NaHCO_3$, MeCN–H_2O (4:1), 0 °C, 10 min, 75%.

In conclusion, this work presents an overview of the potential of the SAD reaction as a tool for accessing 2,4-dimethylpentane-1,2,5-triol motifs or to similar systems often found in biologically active natural products. To this aim, the performance of the SAD reaction of chiral PMB or PMP ether of bishomoallylic alcohols was evaluated in double diastereoselection. If limitations appeared when reactions are performed under mismatched conditions, on the contrary very high levels of matched diastereoselectivity were obtained employing the pyrimidine class of li-



Scheme 6 Synthesis of diol **20**. *Reagents and conditions*: (a) CuI, Me_2C=CH-MgBr, THF, –78 °C to r.t., 12 h, 95%.

gands. Noteworthy, with the PMP protecting group, the reaction rate is significantly increased. Finally, an effective application to the stereoselective synthesis of the C1–C10–C5 fragment of FR225654 has been achieved.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) Typical Procedure for the Sharpless Asymmetric Dihydroxylation
K_2CO_3 (415 mg, 3 mmol), $K_3Fe(CN)_6$ (1.18 g, 3 mol), $K_2OsO_2(OH)_4$ (4 mg, 0.01 mmol), ligand (0.025 mol), and $MeSO_2NH_2$ (95 mg, 1 mmol) were added to a vigorously magnetically stirred solution of olefin (1 mmol) in a 1:1 mixture of *t*-BuOH–H_2O (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C and monitored by TLC. Upon completion, the reaction mixture was quenched with solid Na_2SO_3 (1.5 g), warmed to r.t., and stirred for an additional 60 min. The product was extracted with EtOAc, washed with brine, dried over $MgSO_4$, concentrated, and purified on silica gel to afford an inseparable mixture of the required diol and the corresponding diastereomer.
Spectroscopic Data of Diol 14 (Major Isomer)
^{1}H NMR (300 MHz, CDCl3): δ = 7.26 (d, *J* = 8.6 Hz, 2 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 4.47 (s, 2 H), 3.80 (s, 3 H), 3.42 (dd, *J* = 4.2, 9.0 Hz, 1 H), 3.38 (d, *J* = 12.0 Hz, 1 H), 3.32 (d, *J* = 12.0 Hz, 1 H), 3.21 (m, 1 H), 2.11 (m, 1 H), 1.68 (dd, *J* = 7.8, 14.6 Hz, 1 H), 1.36 (dd, *J* = 3.3, 14.6 Hz, 1 H), 1.16 (s, 3 H), 0.93 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl3): δ = 159.1, 12 9.3, 113.7, 76.6, 72.8, 71.8, 70.9, 55.0, 4 4.3, 28.6, 23.5, 19.5 ppm.
Spectroscopic Data of Diol 16 (Minor Isomer)
^{1}H NMR (300 MHz, CDCl3): δ = 7.26 (d, *J* = 8.6 Hz, 2 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 4. 46 (s, 2 H), 3.80 (s, 3 H), 3.48 (m, 1 H), 3.38 (d, *J* = 11.0 Hz, 1 H), 3.32 (d, *J* = 11.0 Hz, 1 H), 3.19 (m, 1 H), 1.95 (m, 1 H), 1.63 (dd, *J* = 6.0, 14.4 Hz, 1 H), 1.45 (dd, *J* = 4.8, 14.4 Hz, 1 H), 1.16 (s, 3 H), 0.95 (d, *J* = 6 . 9 Hz, 3 H) ppm. 13C NMR (75 MHz, CDCl3) δ = 159.1, 129.3, 113.7, 76.4, 72.6, 71.8, 69.0, 55.0, 44.0, 29.1, 24.3, 19.3 ppm. IR (neat): ν = 3360, 2932, 1611, 1513, 1462, 1246, 1033, 819, 771 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{15}H_{24}NaO_4^+$ [MNa^+]: 291.1567; found: 291.1570.
For spectroscopic data of all diols, see the Supporting Information.

(11) For the synthesis of (*S*)- and (*R*)-iodides **13**, see for instance: (a) Heckrodt, T. J.; Mulzer, J. *Synthesis* **2002**, 1857. (b) Haslett, G. W.; Paterson, I. *Org. Lett.* **2013**, *15*, 1338. (c) For the typical procedure and spectroscopic data of substrates, see the Supporting Information.

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(13) For analytical data for **12** and **13**, see the Supporting Information.

(14) For the osmylation of (*R*)- and (*S*)-**12** and (*R*)- and (*S*)-**13** in the absence of chiral ligands, see general procedure (ref. 10), however, without ligand.

(15) **Analytical Data for 25**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.28–4.01 (br s, 2 H), 3.56 (dd, *J* = 3.6, 10.5 Hz, 1 H), 3.27 (dd, *J* = 9.0, 10.5 Hz, 1 H), 2.40 (d, *J* = 16.8 Hz, 1 Hz), 2.33 (d, *J* = 16.8 Hz, 1 H), 1.93 (m, 1 H), 1.58 (m, 2 H), 1.28 (s, 3 H), 0.86 (d, *J* = 6.9 Hz, 3 H), 0.13 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 103.7, 87.9, 71.7, 68.9, 47.3, 36.1, 31.8, 25.4, 19.6, 0.1 ppm. IR (neat): ν = 3276, 2958, 2927, 2175, 1460, 1423, 1376, 1248, 1032, 758 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{12}H_{24}NaO_2Si^+$ [MNa^+]: 251.1438; found: 251.1439. The relative configuration of **25** was confirmed by NMR experiments (NOESY analysis) of the corresponding γ-lactone (Figure 2).

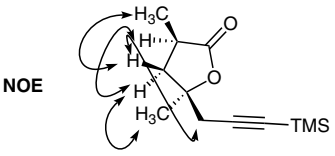

Figure 2