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New S,O-acetals from (1*R*)-(−)-myrtenal as chiral auxiliaries in nucleophilic additions

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Abstract—Treatment of hydroxythiol **4** with α,α-diethoxyacetophenone at room temperature yielded a mixture of epimeric S,O-acetals **6** and **7** (1:4, 92% yield), which were efficiently separated by flash chromatography. The OTBS derivatives **8** and **9** were treated with several Grignard reagents to afford carbinols **10** and **13** respectively (85–99% yield, >95% dr). After successive hydrolysis and reduction of 10 and 13 it is possible to obtain either enantiomer of diols **16** in high optical purity (>95% er).

As part of our research to develop new chiral auxiliaries, we described the synthesis of 2-acyl-1,3-oxathianes,[1] which have been proven as useful synthetic tools for the enantioselective preparation of several chiral 1,1-dialkyl-1,2-ethanodiols.[2] These compounds are key intermediates for constructing chiral α-hydroxycarbonyl derivatives possessing important biological activities (Chart 1).[3] In the precedent papers[1,2] of this series we described the synthesis of oxathiane **1** and acyloxathianes **2a** and **2b** in 35%, 45%, and 32% isolated yield, respectively (Chart 1). Further, in a recent work Solladié-Cavallo et al. described the synthesis of 2-substituted alkyl oxathianes by condensing the anion of oxathiane **1** with acetaldehyde and benzaldehyde.[4] The

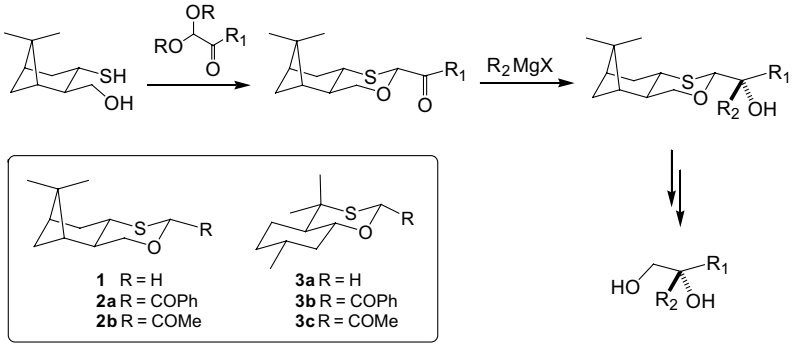

Chart 1.

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successful preparation of the anion of oxathiane **1** and its condensation with several electrophiles[4] added synthetic value to oxathiane **1** because it enhances the possibility to obtain a major variety of enantiomerically pure α-hydroxycarbonyl derivatives. In spite of the almost quantitative preparation of hydroxythiol **4** (Scheme 1) from (1*R*)-(−)-myrtenal,[1,2] chemical yields of oxathiane **1** and acyloxathianes **2a** and **2b**, ranging 35–45%, remained as a challenge to be improved. This work presents recent advances in this direction, and the use of new S,O-acetals as chiral auxiliaries to be used in pursuing the same molecular targets obtained by using oxathianes **1** and **3a**, and acyloxathianes **2a**,**b** and **3b**,**c** prepared by us[1,2] and by Eliel's group,[5] respectively.

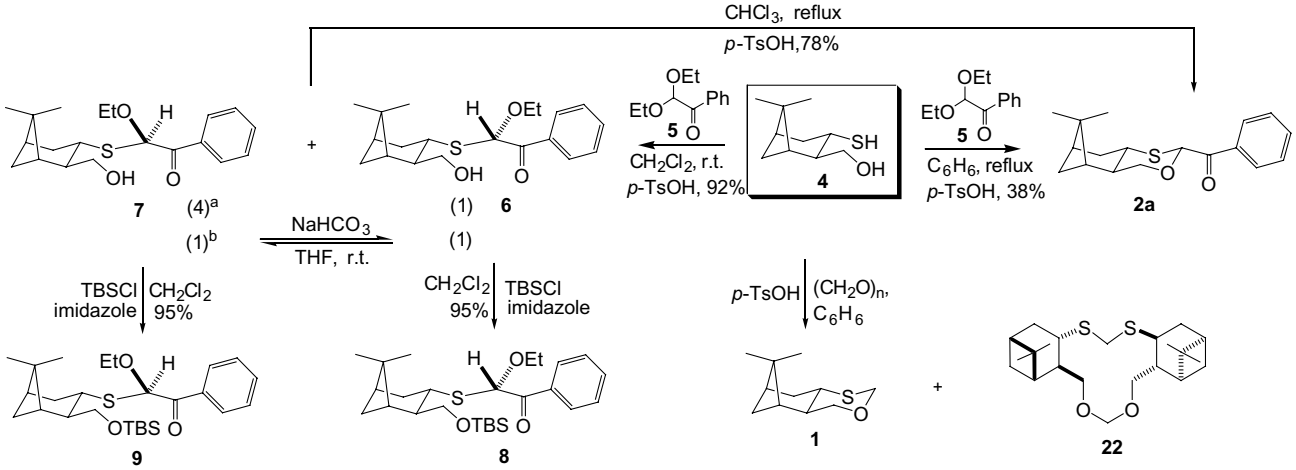
In a search to improve the chemical yield of benzoyloxathiane **2a**, we carried out the coupling of hydroxythiol **4** with α-ketoacetal **5** in CH_2Cl_2 at room temperature using *p*-TsOH as catalyst, affording, almost quantitatively, the S,O-acetals **6** and **7** in 1:4 ratio, which were readily separated by flash chromatography (**6**: R_f 0.16; **7**: *rf* 0.25; TLC, hexane–EtOAc 4:1). The reaction outcome was easily equaled to 1:1 by treated the original mixture with $NaHCO_3$ in THF at room temperature (Scheme 1).

The structural analogy of these compounds with oxathiane **2a** is evident; therefore this finding encouraged us to evaluate them as chiral auxiliaries in diastereoselective additions to their keto group, as was done for oxathianes **2a** and **2b**.[1,2] In order to achieve such additions, the OH group of S,O-acetals **6** and **7** was protected with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole in anhydrous CH_2Cl_2, giving the nonequilibrated S,O-acetals **8** (R_f 0.84; hexane–EtOAc 9:1) and **9** (R_f 0.79 in TLC; hexane/EtOAc 9:1) in 95%.[6] It is worth noting that R_f values of **8** and **9** are closer than those of the unprotected S,O-acetals **6** and **7**; nevertheless, these compounds are efficiently separated by flash or radial chromatography.[7] In addition, the reversed polarity in TLC of S,O-acetals **8** and **9**, with regard to S,O-acetals **6** and **7**, should be noted.[8]

The OTBS derivatives **8** and **9** were treated with several representative nucleophiles, giving the corresponding adducts **10a**–**g** and **11a**–**g** (Table 1), as well as **12a**,**b**,**e** and **13a**,**b**,**e**, respectively.[9] As can be seen, diastereoselective ratios were excellent with Grignard reagents, and are similar to those described for acyloxathianes **2a** and **2b**.[1,2] As described in additions to acyloxathianes **2a** and **2b**, a small amount of alcohol **10g** was detected in the above reactions.[10] The higher stereoselectivities shown with Grignard reagents, as compared to those with *n*-BuLi and $LiAlH_4$ (entries 7 and 8) agree with the ability of the metal to form C=O–M–O interactions, which in turn favor the formation of the highly stereoselective Cram chelated transition state.[11]

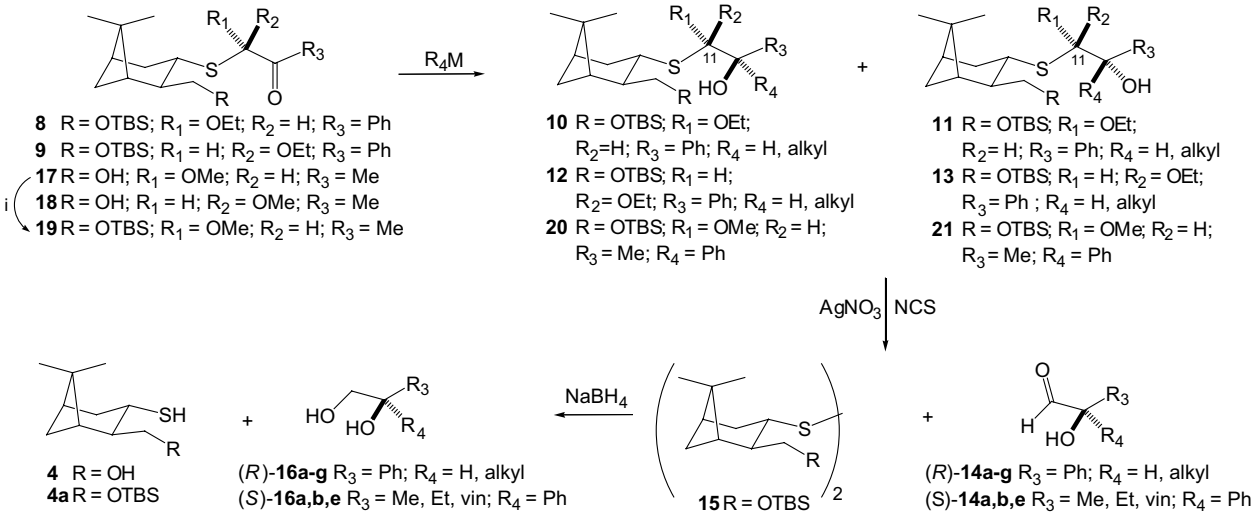
The absolute configuration of the new stereogenic center was established by chemical correlation with compounds of known absolute stereochemistry. Thus, the oxidative hydrolysis of adducts **10a**–**g** proceeded in 80–95% yielding mixtures of the corresponding α-hydroxyaldehydes (*R*)-**14a**–**g** with the dimeric disulfide **15**, which is favored over the expected sultine[12] due to angular strain. The reduction of this mixture with $LiAlH_4$, or $NaBH_4$, followed by flash chromatography, provided the corresponding diols **16a**–**g** (85–93% yield) and regenerated hydroxythiol **4**, or the OTBS protected thiol **4a** (75–85% yield).[13] The optical rotations of diols **16a**–**g** were compared with those previously described, allowing to know both their optical purity and absolute configuration, which was established as (*R*).[2,14a–c] Complementarily, Ag_2O oxidation of the reaction mixture of (*R*)-**14a** and **15** afforded (*R*)-(−)-atrolactic acid and the nonfurther oxidized disulfide **15**. This chemical correlation, together with that of diols (*R*)-**16a**–**b**, also constitutes evidence for the absolute configuration of the nonisolated aldehydes **14a**–**g**.

In order to gain further stereochemical information concerning diastereoselectivities, adducts **13a**,**b**,**e** were also submitted to hydrolysis, giving aldehydes (*S*)-**14a**,**b**,**e** and dimer **15**. These aldehydes were efficiently reduced with $NaBH_4$ to the corresponding diols (*S*)-



Scheme 1. Preparation of S,O-acetals **8** and **9** from hydroxythiol **4**, which is a key precursor for the synthesis of chiral auxiliaries **1** and **2a**. Numbers in parentheses indicate the **6**:**7** ratio: [a]obtained from the crude reaction, and [b]after equilibration with $NaHCO_3$.

Table 1. Use of S,O-acetals as chiral auxiliaries in diastereoselective nucleophilic additions and its chemical correlation with diols of known absolute configuration



Entry	S,O-Acetal	R_4M	R_4	Adducts (% ratio, % yield)[a]	Diol, % yield[b]	Abs. config., % Er[f]
1	**8**	MeMgBr	Me	**10a**:**11a** (>99:1, 99)	**16a**, 90	(*R*), >95
2	**8**	EtMgBr	Et	**10b**:**11b** (>99:1, 99)	**16b**, 86	(*R*), >95
3	**8**	*i*-PrMgBr	*i*-Pr	**10c**:**11c** (>99:1, 74)[c]	**16c**, 72	(*R*), >95
4	**8**	*i*-BuMgBr	*i*-Bu	**10d**:**11d** (>99:1, 82)[c]	**16d**, 76	(*R*), >95
5	**8**	CH_2=CHMgBr	CH_2=CH	**10e**:**11e** (>99:1, 88)	**16e**, 88	(*R*), >95
6	**8**	MeLi	Me	**10a**:**11a** (>99:1, 99)[d]	**16a**, 82	(*R*), >95
7	**8**	*n*-BuLi	*n*-Bu	**10f**:**11f** (>90:10, 74)	**16f**, 63	(*R*), 89
8	**8**	$LiAlH_4$	H	**10g**:**11g** (80:20, 96)	**16g**, 68	(*R*), 80
9	**9**	MeMgBr	Me	**12a**:**13a** (1:>99, 99)	**16a**, 92	(*S*), >95
10	**9**	EtMgBr	Et	**12b**:**13b** (1:>99, 99)	**16b**, 90	(*S*), >95
11	**9**	CH_2=CHMgBr	CH_2=CH	**12e**:**13e** (1:>99, 86)	**16e**, 85	(*S*), >95
12	**19**	PhMgBr	Ph	**20**:**21** (>99:1, 96)[e]	**16a**, 76	(*S*), >95

[a] The ratio was measured by integrating H-11 in the NMR (300 MHz) spectra of the crude reaction mixture, and the yield was calculated as the mixture of both diastereomers.

[b] Calculated from the hydrolysis of the precursor adducts.

[c] Chemical yield was diminished due to the formation of adduct **10g** as by-product.

[d] MeLi gave the same adduct as MeMgBr starting with **8**.

[e] Only S,O-acetal **19** was treated with PhMgBr to corroborate the stereochemistry at C-11 of compounds **17** and **18**. At scheme (i) **17** → **19**: TBSCl, imidazole, CH_2Cl_2, rt, 95% yield.

[f] Absolute configuration and % er were determined according to Refs. 2,14a–c.

16a,**b**,**e**. Once the absolute configuration of diols (*R*)-**16a**–**g** and (*S*)-**16a**,**b**,**e** were known from their optical rotations,[2,14a] it was possible to assign the absolute configuration at C-11 of S,O-acetals **6** and **7**, being (*S*) and (*R*), respectively. This finding was further sustained by assuming that nucleophilic additions on **8** and **9** took place in agreement with the Cram chelated mechanism, as is observed in acyloxathianes.[1,2,5] In this sense, the higher conformational freedom of S,O-acetals **8** and **9**, as compared to acyloxathianes, seems not to be an obstacle to attain a chelated transition state. Nevertheless, such conformational freedom could be responsible for the larger tendency of **8** and **9** to be epimerized in comparison to acyloxathianes.[9] In other words, the corresponding anions of **8** and **9**, which presumably are formed before the nucleophilic addition takes place, cannot reach the typical equatorial preference[15] as can anions of oxathianes **1**[4] and **3a**,[16] since the former are acyclic S,O-thioacetals and the later are cyclic S,O-thioacetals. This means that anions of **8** and **9**, or **6** and **7** are probably quite close in energy.

In order to extend the scope for the formation of S,O-acetals, treatment of hydroxythiol **4** with pyruvic aldehyde dimethyl acetal under the above reaction condition, led to a 2:1 mixture of S,O-acetals **17** and **18**, respectively, in 95% yield. In spite of their close *rf* values (**17**, R_f 0.20; **18**, R_f 0.26; hexane–EtOAc 7:3) they were efficiently separated by radial chromatography. Thus, diastereomerically pure S,O-acetal **17** was also treated with TBSCl affording the protected S,O-acetal **19** in 95% yield. Following the same reaction conditions used to obtain adducts **10a**–**g**, compound **19** was treated with PhMgBr yielding adducts **20** and **21** in >99:1 ratio and 96% yield. The hydrolysis of adduct **20**, and subsequent reduction of the intermediate aldehyde (*S*)-**14a**, (Table 1,

entry 12) led to diol (*S*)-**16a**, which possesses the same configuration as diol obtained from adduct **13a** (Table 1, entry 9). Therefore, and as was stated for S,O-acetals **6** and **7**, this result indicates that the stereochemistry at C-11 in S,O-acetals **17** and **18** is (*S*) and (*R*), respectively. It is noteworthy that S,O-acetals **8** ($R_3 = Ph$) and **19** ($R_3 = Me$) afford the α-hydroxycarbonyl derivatives possessing the opposite absolute configuration than those obtained with oxathianes **2a** and **3b**, or oxathianes **2b** and **3c**, respectively. This fact represents a synthetic complement when acyloxathianes are used as chiral auxiliaries, since to obtain a given enantiomeric pair it was necessary to interchange the R group of the acyl moiety followed by addition of the appropriate Grignard reagent.[5]

Although the chiral auxiliary is recovered in good yield, either as **4**, **4a** or **15**, the main shortcoming of this methodology is that in the next cycle of induction, when reusing the chiral auxiliary **4**, the separation of S,O-acetals **6** and **7** (when using **4**), or **8** and **9** (if **4a** is used) should be faced. Therefore, at that stage it should be decided if equilibration of the crude mixture of **6** and **7** will be carried out or not, depending on the desired absolute configuration of the target compound.

On the other hand, taking advantage of the isolation of S,O-acetals **6** and **7**, and assuming their intermediacy in the formation of oxathiane **2a**, they were converted to the last compound in 78% isolated yield by refluxing in $CHCl_3$ in the presence of *p*-TsOH during 1 h (Scheme 1). This result is a notable yield improvement concerning the synthesis of benzoyloxathiane **2a**.

From the last reaction were isolated dimeric compounds[17] in roughly 10% yield, which are structurally related to dimer **22** isolated from the treatment of hydroxythiol **4** with paraformaldehyde (Scheme 1).[4,18] As mentioned above, such behavior could be explained in terms of angular strain. In other words, the lower conformational freedom of hydroxythiol **4**, that is, as compared to hydroxythiol prepared from pulegone,[5] partially precludes the formation of an additional ring (in this case the oxathiane ring), affording dimeric compounds with less content of angular strain. This is the reason why dimer **15** is likely formed in lieu of the sultine,[12] which was not previously isolated.[1,2]

In search to improve the synthesis of acetyloxathiane **2b**, the above protocol was applied to the crude mixture of S,O-acetals **17** and **18**. However, in this case the yield of the desired oxathiane **2b** resulted similar to that described without previous isolation of S,O-acetals **17** and **18**.[1]

In conclusion, the synthesis of S,O-acetals **6**, **7**, **17**, and **18** provides clear evidence that our experimental protocol can be extended to the preparation of a wide variety of analogous S,O-acetals. In addition, was demonstrated that such compounds represent an attractive synthetic alternative to prepare the some times desirable enantiomeric pair of molecules in high optical purity. Finally, was demonstrated that the isolation of the above S,O-acetals are opening a new avenue to substantially improve the synthesis of the corresponding acyloxathianes. Spectroscopic data for compounds **8** and **10a** are showed.[19,20]

Acknowledgements

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6. Starting from diastereomerically pure S,O-acetal, certain degree of epimerization at C-11 is observed when CH_2Cl_2 is not anhydrous. OTBS protection in DMF as solvent should also be avoided due to epimerization of pure S,O-acetal.
7. S,O-Acetals **6** and **7** are easier separated by flash chromatography than compounds **8** and **9** because their larger R_f value differences; however, the later can be efficiently separated by applying the following typical procedure: In a chromatography column (id = 3.5 cm) packed with 90 cm of flash silica gel, 584 mg of the crude mixture of S,O-acetals **8** and **9** were eluted with a mixture of EtOAc–hexane (1:49) at 15 psi, giving 344 mg (59%) of **8**, 192 mg (33%) of **9** and 46 mg (8%) of a mixture of both compounds.
8. This was corroborated by converting diastereomerically pure **6**–**8** and comparing its R_f values with the crude mixture of **8** and **9**.
9. Grignard reagents should be freshly prepared; otherwise epimerization of pure **8** or **9** at C-11 occurs before addition takes place, affording mixtures of adducts **10** and **11**, or **12** and **13**, respectively, in unpredictable ratios.
10. This by-product is formed by hydride transfer from the β-position of the Grignard reagent: Hamelin, A. *Bull. Soc. Chim. Fr.* **1961**, 1211.
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12. The expected sultine would be 9,9-dimethyl-4-oxa-5-thia-tricyclo[6.1.1.0 [2,6]]decane 5-oxide.
13. The reduction of the mixture of aldehydes **13** and dimer **15** with $NaBH_4$ provides the corresponding diol and thiol **4a**; however, when $LiAlH_4$ is used, hydroxythiol **4** and the corresponding diol are obtained.
14. (a) **16a**–**c**,**e**: Colombo, L.; Di Giacomo, M.; Brusotti, G.; Milano, E. *Tetrahedron Lett.* **1995**, 2863; (b) **16g**: Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1970**, *35*, 4002; (c) Gaul, C.; Schärer, K.; Seebach, D. *J. Org. Chem.* **2001**, *66*, 3059.
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18. In fact, spectroscopic and X-ray data of this dimer were described: Vargas-Díaz, M. E. M. Sc. dissertation, Escuela Nacional de Ciencias Biológicas-IPN, Mexico City, 2002.
19. Compound **8**: $[\alpha]_D^{28}$ −4.4° (*c* 0.40, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10–7.40 (m, 5H, Ar), 5.84 (s, 1H, H-11), 4.01 (dq, 1H, J = 9.2, 7.2 Hz, OCHa), 3.60 (dq, 1H, J = 9.2, 7.2 Hz, OCHb), 3.38 (t, 1H, J = 10.0 Hz, H-10a), 3.20 (dd, 1H, J = 10.0, 4.2 Hz, H-10b), 2.85 (m, 1H, H-3), 2.77 (m, 1H, H-4eq), 2.38 (m, 1H, H-7eq), 2.18 (m, 1H, H-5), 2.11 (ddd, 1H, J = 13.8, 5.9, 2.4 Hz, H-4ax), 1.91 (m, 1H, H-1), 1.86 (m, 1H, H-2), 1.29 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.17 (s, 3H, Me-9), 0.98 (s, 3H, Me-8), 0.94 (d, 1H, J = 10.0 Hz, H-7ax), 0.77 (s, 9H, *t*-Bu), −0.12 (s, 3H, Me–Si), −0.14 ppm (s, 3H, Me–Si). IR (CH_2Cl_2): ν_{max} 3059, 2926, 2857, 1686, 1597, 1579, 1250, 1087.2, 836.2, 776 cm^{-1}. MS *m*/*z*: 357 (M^+−105, 8), 135 (100), 133 (16), 105 (44), 79 (93), 41 (19), 29 (18). Calcd for $C_{26}H_{42}O_3SSi$: C, 67.51; H, 9.09; S, 6.92. Found: C, 67.69; H, 8.83; S, 7.20.
20. Compound **10a**: $[\alpha]_D^{24}$ +25.7° (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H, Ar), 4.59 (s, 1H, H-11), 3.88 (dq, 1H, J = 9.9, 7.1 Hz, OCHa), 3.65 (dd, 1H, J = 9.9, 4.7 Hz, H-10b), 3.54 (t, 1H, J = 10.0 Hz, H-10a), 3.26 (dq, 1H, J = 9.9, 7.1 Hz, OCHb), 3.17 (br s, 1H, OH), 2.95 (m, 1H, H-3), 2.50–2.31 (m, 2H, H-4eq, H-7eq), 2.19 (m, 1H, H-1), 2.12–1.86 (m, 3H, H-5, H-4ax, H-2), 1.62 (s, 3H, Me-13), 1.19 (s, 3H, Me-9), 1.13 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.17 (s, 3H, Me-9), 0.99 (d, 1H, J = 9.8 Hz, H-7ax), 0.90 (s, 3H, Me-8), 0.88 (s, 9H, *t*-Bu), 0.03 (s, 3H, Me–Si), 0.02 ppm (s, 3H, Me–Si). IR (CH_2Cl_2): ν_{max} 3467, 2928, 2857, 1447, 1079, 699, 620 cm^{-1}. LRMS (EI) *m*/*z*: 460 (M^+−18, 1), 375 (21), 357 (57), 135 (100), 133 (71), 105 (58), 73 (36). HRMS (FAB^+) calcd for $C_{27}H_{46}O_3SSiNa$: 501.2835, found: 501.2827.