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Regioselective Reductive Heck Arylation of a Rigid Tetracyclic Oxanorbornene Scaffold

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Abstract—Reductive Heck arylation of the tetracyclic oxanorbornene (**1**) was found to proceed with complete regioselectivity. A number of aryl iodides were investigated, all giving the same selectivity. Modifications within the scaffold were also tested, giving a 84:16 ratio of regioisomers in the worst case. The regioselectivity is probably due to steric factors.

Introduction

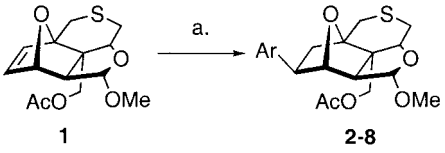
Synthetic methods with a high regio- or stereoselectivity are of great importance in applications of all kinds of organic synthesis. We would here like to report a reductive Heck arylation which gives complete regio- and stereoselectivity on the tetracyclic oxanorbornene **1**.[1] The reductive Heck arylation of norbornenes has proved to be an effective method for synthesis of bicyclo[2.2.1]heptanes with an aromatic group in the *exo* configuration.[2,3] It has been used in total synthesis of the alkaloid epibatedine[4] as well as in different approaches for analogues thereof.[5,6] Exclusive attack at the *exo* face is well known in bicyclic systems,[7] the regioselectivity in our work with **1** as substrate was, however, unexpected.

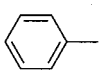
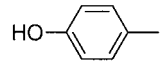
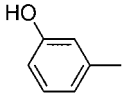
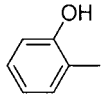
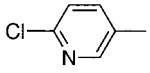
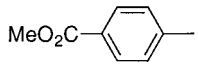
Results and Discussion

The oxanorbornene **1**[1] was treated with iodobenzene, piperidine and formic acid in presence of $Pd(OAc)_2(PPh_3)_2$ according to the published procedure[2] and yielded **2** (74%) as one regioisomer (Table 1). The regioselectivity upon arylation of **1** was independent of the aryl iodide; only one isomer was detected by NMR when the reaction was performed with 4-iodophenol (giving **3** in 81% yield), 3-iodophenol (**4**, 77%) and 2-iodophenol (**5**, 82%), 2-iodothiophene (**6**, 67%), 2-chloro-5-iodopyridine [8,9] (**7**, 81%) and methyl 4-iodobenzoic ester (**8**, 80%) (Table 1).

Variations within the tetracyclic scaffold were then investigated. The sulfone **9**[1] gave compound **10** (76%) as one regioisomer, and compound **12** synthesized from **11**[1]

Table 1. Only one regioisomer was formed in reductive Heck arylation of **1** with different aryl iodides



Compound	Ar—	Yield
2		74%
3		81%
4		77%
5		82%
6		67%
7		81%
8		80%

a: ArI, $Pd(OAc)_2(PPh_3)_2$, piperidine, HCO_2H, DMF, 50°C, overnight.

Keywords: regioselective; Heck reactions; arylation; conformationally rigid compounds.

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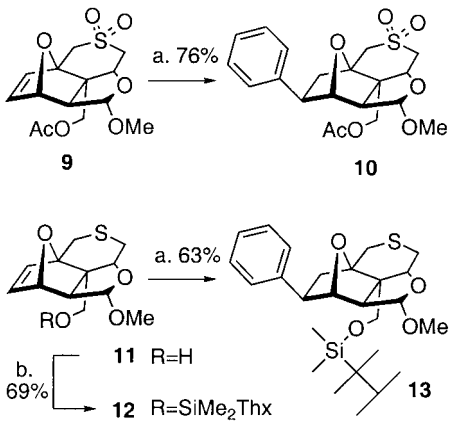


Scheme 1. Tetracyclic oxanorbornenes **9** and **12** gave only one regioisomer in reductive Heck arylation. (a) PhI, $Pd(OAc)_2(PPh_3)_2$, piperidine, HCO_2H, DMF, 50°C, overnight. (b) $Me_2ThxSiCl$, imidazole, DMF, room temperature, overnight.

(69%) gave compound **13** (63%) with complete regioselectivity (Scheme 1).

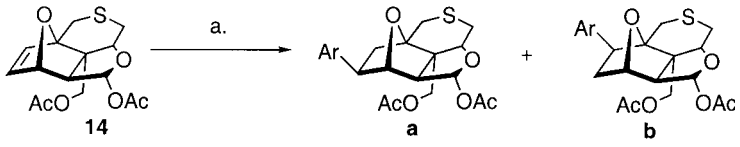
However, the reductive Heck arylation, performed with iodobenzene on the diacetate **14**[10] yielded **15ab** (79%) as a 97:3 mixture of regioisomers and with 4-iodophenol **16ab** (95%) as an 84:16 mixture (Table 2). Furthermore reductive Heck arylation of **14** was tested with the electron poor arylgroup methyl 4-iodobenzoic ester, which yielded **17** (92%) *as one single regioisomer* (Table 2).

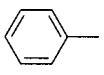
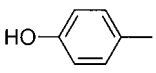
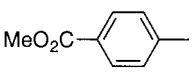
When the tetracycle is substituted with an electron withdrawing group at C-1, reductive Heck arylation gives lower regioselectivity. In addition the regioselectivity is dependent on the aryl iodide: electron rich aryl iodides give lower regioselectivity and electron poor give better.

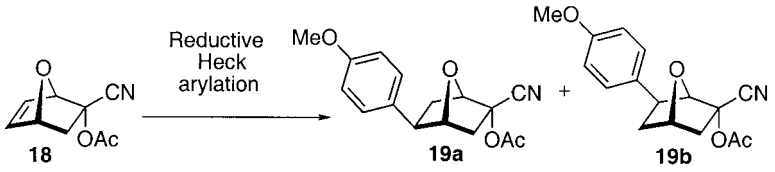
Products were isolated with flash chromatography and were, with the exception of **15ab** and **16ab**, found to be one pure isomer according to NMR analysis. The configuration was confirmed by the absence of any vicinal coupling between the bridgehead proton and the proton on the carbon bearing the aryl group. The peak of the bridgehead proton was a sharp singlet. The regioisomeric mixtures **15ab** and **16ab** were not separated but ^1H NMR spectra of the major products were easily extracted from the spectra of the mixtures. ^1H NMR spectra of the minor products were not completely resolved, but the configurations of the minor regioisomers are supported by the following data: The minor regioisomers showed the peak of the bridgehead proton (H-3) as a doublet (J approx. 5 Hz) or, if not resolved, as a multiplet. In **16b** one of the protons α to the sulfur atom (H-10) is shifted upfield (from approx. 3.2 ppm to approx. 2.2 ppm) indicating steric repulsion between that proton and one proton on the aromatic ring.

Though high regioselectivities caused by steric factors are well known in non-reductive Heck reactions,[11] there seems to be only one previous example of a regioselective reductive Heck reaction; an isomeric ratio of 84:16 was reported for the bicyclic oxanorbornene **18** (Scheme 2).[12] The reason

Table 2. Yields and regioselectivities in reductive Heck arylations of **14** with different aryl iodides (a: ArI, $Pd(OAc)_2(PPh_3)_2$, piperidine, HCO_2H, DMF, 50°C, overnight)



Starting material	Product	Ar–	Yield (%)	Regioisomeric ratio **a**:**b**
14	**15ab**		79	97:3
14	**16ab**		95	84:16
14	**17**		92	1:0



Scheme 2. A 84:16 mixture of regioisomers **19a**:**19b** was reported in reductive Heck arylation of **18**.

for the regioselectivity in this case is obviously not steric; instead it seems plausible that electron withdrawing acetate and cyano groups effect the polarization of the double bond.

Though the regioselectivity in reductive Heck arylation of **14** to some extent appears to be dependent on electronic factors, the main reason for the regioselectivity is most likely steric factors. Steric repulsion between one of the hydrogen atoms α to the sulfur atom and a hydrogen atom on the aromatic ring in the transition state of the carbon–carbon bond forming step probably prevents formation of the absent (minor) regioisomer.

Experimental

General

NMR-spectra were recorded on a Bruker DRX 400 instrument, using $CDCl_3$ as solvent and $CHCl_3$ (^{1}H, δ 7.26) (^{13}C, δ 77.0) as internal standard. TLC analyses were performed with Merck SiO_2 60 F_{256} precoated aluminium sheets with visualisation by UV light and charring with anisaldehyde in ethanolic sulfuric acid. Flash chromatography was performed with Matrex SiO_2 60 (35–70 μm). Commercially available $Pd(OAc)_2(PPh_3)_2$ was used. The reductive Heck arylations were performed as described in the general procedure. For ^{1}H NMR data for **2**–**8**, **10** and **13** see Table 3. For atom numbering for NMR data see Fig. 1.

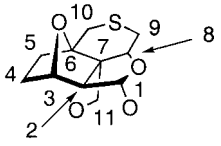


Figure 1. Atom numbering for NMR data.

General procedure for the arylations

Oxanorbornene (16.5 mg, 55 μmol), $Pd(OAc)_2(PPh_3)_2$ (4.1 mg, 5.5 μmol) and aryliodide (220 μmol) were dissolved in dry DMF (200 μl). Piperidine (25 μl, 250 μmol) and formic acid (9 μl, 235 μmol) were added and the reaction mixture was stirred under argon at 50°C until the oxanorbornene was consumed (typically overnight). The reaction mixture was diluted with EtOAc (10 mL) and was washed with water (3 mL). The aqueous phase was extracted with EtOAc (3 mL). The combined organic phases were washed with brine (5 mL) and dried ($MgSO_4$). Flash chromatography (heptane/EtOAc) yielded the product.

(+)-[(1*R*,3*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-Methoxy-3-phenyl-7,13-dioxa-10-thiatetracyclo[6.3.1.1$^{1.4}$.0$^{5.12}$]tridec-12-yl]methyl acetate (2). $[\alpha]_D^{23}=+88$ (*c* 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 170.3 (CO), 145.1 (Ar), 128.6 (Ar), 127.0 (Ar), 126.6 (Ar), 107.9 (C-1), 85.0 (C-3), 83.0 (C-6), 77.6 (C-8), 68.7 (C-11), 61.8 (C-2), 54.5 (OMe), 51.2 (C-7), 49.1 (C-4), 44.7 (C-5), 31.1 (C-10), 29.0 (C-9), 20.9 (OAc). HRMS calcd for $C_{20}H_{24}O_5SNa$ (M+Na): 399.1242, found: 399.1246.

(+)-[(1*R*,3*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-Methoxy-3-(4-phenol)-7,13-dioxa-10-thiatetracyclo[6.3.1.1$^{1.4}$.0$^{5.12}$]tridec-12- yl]-methyl acetate (3). $[\alpha]_D^{23}=+23$ (*c* 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 170.4 (CO), 154.4 (Ar), 137.2 (Ar), 128.1 (Ar), 115.4 (Ar), 107.9 (C-1), 85.2 (C-3), 83.0 (C-6), 77.5 (C-8), 68.7 (C-11), 61.7 (C-2), 54.5 (OMe), 51.2 (C-7), 48.3 (C-4), 44.7 (C-5), 31.1 (C-10), 29.0 (C-9), 20.9 (OAc). HRMS calcd for $C_{20}H_{24}O_6SNa$ (M+Na): 415.1191, found: 415.1196.

(+)-[(1*R*,3*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-Methoxy-3-(3-phenol)-7,13-dioxa-10-thiatetracyclo[6.3.1.1$^{1.4}$.0$^{5.12}$]tridec-12-yl]-methyl acetate (4). $[\alpha]_D^{23}=+73$ (*c* 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 170.4 (CO), 156.1 (Ar), 146.8 (Ar), 129.7 (Ar), 119.4 (Ar), 113.7 (Ar), 107.8 (C-1), 84.9 (C-3), 83.1 (C-6), 77.5 (C-8), 68.7 (C-11), 61.7 (C-2), 54.5 (OMe), 51.2 (C-7), 48.9 (C-4), 44.4 (C-5), 31.1 (C-10), 29.0 (C-9), 20.9 (OAc). HRMS calcd for $C_{20}H_{24}O_6SNa$ (M+Na): 415.1191, found: 415.1187.

(+)-[(1*R*,3*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-Methoxy-3-(2-phenol)-7,13-dioxa-10-thiatetracyclo[6.3.1.1$^{1.4}$.0$^{5.12}$]tridec-12-yl]-methyl acetate (5). $[\alpha]_D^{24}=+68$ (*c* 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 170.2 (CO), 154.4 (Ar), 130.3 (Ar), 128.8 (Ar), 127.3 (Ar), 119.6 (Ar), 117.8 (Ar), 107.5 (C-1), 85.5 (C-6), 83.7 (C-3), 77.2 (C-8), 68.4 (C-11), 61.1 (C-2), 54.6 (OMe), 50.8 (C-7), 48.9 (C-4), 40.8 (C-5), 30.7 (C-10), 28.9 (C-9), 20.8 (OAc). HRMS calcd for $C_{20}H_{24}O_6SNa$ (M+Na): 415.1191, found: 415.1189.

(+)-[(1*R*,3*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-Methoxy-7,13-dioxa-3-(2-thiophene)-10-thiatetracyclo[6.3.1.1$^{1.4}$.0$^{5.12}$]tridec-12-yl] methyl acetate (6). $[\alpha]_D^{23}=+76$ (*c* 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 170.2 (CO), 148.1 (Ar), 126.6 (Ar), 123.7 (Ar), 123.3 (Ar), 107.7 (C-1), 85.1 (C-3), 83.3 (C-6), 77.6 (C-8), 68.5 (C-11), 61.2 (C-2), 54.5 (OMe), 50.9 (C-7), 44.8 (C-5), 44.5 (C-4), 30.9 (C-10), 28.9 (C-9), 20.8 (OAc). HRMS calcd for $C_{18}H_{22}O_5S_2Na$ (M+Na): 405.0806, found: 405.0821.

(+)-[(1*R*,3*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-3-(6-Chloro-3-pyridinyl)-6-methoxy-7,13-dioxa-10-thiatetracyclo[6.3.1.1$^{1.4}$.0$^{5.12}$]-tridec-12-yl]methyl acetate (7). $[\alpha]_D^{23}=+76$ (*c* 0.77, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 170.2 (CO), 149.9 (Ar), 148.3 (Ar), 139.5 (Ar), 137.2 (Ar), 124.6 (Ar), 107.6 (C-1), 84.6 (C-3), 83.5 (C-6), 77.5 (C-8), 68.4 (C-11), 61.5 (C-2), 54.5 (OMe), 51.2 (C-7), 45.8 (C-4), 44.6 (C-5), 31.0 (C-10), 28.9 (C-9), 20.9 (OAc). HRMS calcd for $C_{19}H_{22}O_5SNClNa$ (M+Na): 434.0805, found: 434.0815.

(+)-[(1*R*,3*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-Methoxy-3-(4-methyl benzoic ester)-7,13-dioxa-10-thiatetracyclo[6.3.1.1$^{1.4}$.0$^{5.12}$]tridec-12-yl] methyl acetate (8). $[\alpha]_D^{23}=+73$ (*c* 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 170.2 (CO), 166.9 (CO), 150.2 (Ar), 130.0 (Ar), 128.5 (Ar), 127.0 (Ar), 107.8 (C-1), 84.5 (C-3), 83.2 (C-6), 77.5 (C-8), 68.6 (C-11), 61.7 (C-2), 54.5 (CO_2Me), 52.0 (OMe), 51.2 (C-7), 49.1 (C-4), 44.5 (C-5), 31.0 (C-10), 29.0 (C-9), 20.8 (OAc). HRMS calcd for $C_{22}H_{26}O_7SNa$ (M+Na): 457.1297, found: 457.1280.

(+)-[(1*R*,3*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-Methoxy-3-phenyl-7,10,10,13-tetraoxa-10-thiatetracyclo[6.3.1.1$^{1.4}$.0$^{5.12}$]tridec-12-yl] methyl acetate (10). $[\alpha]_D^{23}=+49$ (*c* 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 170.1 (CO), 143.9 (Ar), 128.7 (Ar), 127.0 (Ar), 107.8 (C-1), 86.3 (C-6), 85.6 (C-3), 79.9 (C-8), 67.8

Table 3. ^{1}H NMR (solvent: $CDCl_3$) chemical shifts (ppm), signal multiplicities and coupling constants (Hz)

Proton[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**13**
1	4.95 s	4.93 s	4.94 s	5.00 s	4.94 s	4.95 s	4.95 s	4.98 s	4.91 s
2	2.21 s	2.18 s	2.19 s	2.31 s	2.20 s	2.22 s	2.21 s	2.31 s	2.00 s
3	4.50 s	4.40 s	4.47 s	4.66 s	4.48 s	4.45 s	4.49 s	4.59 s	4.44 s
4*endo*	2.94 dd	2.87 dd	2.89 dd	3.06 dd	3.30 dd	2.98 dd	3.00 dd	2.93 dd	2.89 dd
5*endo*	2.47 dd	2.43 dd	2.43 dd	2.43 dd	2.50 dd	2.56 dd	2.49 dd	2.63 dd	2.56 dd
5*exo*	1.45 dd	1.39 dd	1.44 dd	1.72 dd	1.52 dd	1.34 dd	1.42 dd	1.55 dd	1.43 dd
8	4.26 t	4.26 t	4.26 t	4.28 t	4.25 t	4.27 t	4.26 t	4.63 t	4.20 t
9ax		3.14 dd	3.14 dd	3.16 dd	3.12 dd	3.15 dd		3.44 dd	3.27 m
10ax		3.12 d	3.13 d	3.19 d	3.11 d	3.13 d		3.54 d	3.30 d
9eq		2.97 ddd	2.97 m		2.96 ddd	2.97 m	2.97 m	3.68 ddd	2.91 m
10eq		2.87 m	2.86 m		2.88 dd	2.86 dd	2.89 d	3.64 dd	2.81 dd
9,10ax	3.18–3.11 m						3.18–3.10 m		
9,10eq	3.01–2.85 m			3.02–2.93 m					
11	4.36/4.33 ABq	4.35/4.31 ABq	4.35/4.30 ABq	4.38/4.33 ABq	4.35/4.27 ABq	4.36/4.31 ABq	4.36/4.32 ABq	4.51/4.36 ABq	3.85 s
Ar	7.30–7.26 m	7.12 m	7.12 t	7.14 m	7.12 dd	8.24 d	7.94 d	7.32–7.20 m	7.32–7.25 m
Ar	7.24–7.18 m	6.75 m	6.78 m	6.94 dd	6.90 dd	7.66 dd	7.34 d		7.22–7.17 m
Ar			6.69 m	6.88 d	6.84 m	7.27 d			
Ar				6.77 dt					
OMe	3.31 s	3.31 s	3.31 s	3.32 s	3.31 s	3.31 s	3.30 s	3.33 s	3.33 s
OAc	2.12 s	2.12 s	2.12 s	2.13 s	2.12 s	2.13 s	2.12 s	2.14 s	
Other		5.32 br s OH	5.63 br s OH	8.06 s OH			3.89 s Ester		1.64 sept. CH 0.89 d Me 0.87 s Me
Coupling constants									0.14 s SiMe
J1-2	0	0	0	0	0	0	0	0	0
J2-3	0	0	0	0	0	0	0	0	0
J4en-5en	8.5	8.5	8.5	8.9	8.5	8.5	8.5	8.6	8.5
J4en-5ex	6.3	6.3	6.3	6.5	6.0	6.1	6.3	6.0	6.3
J5en-5ex	13.0	13.0	13.0	13.6	13.1	13.2	13.0	13.2	12.8
J8-9	3.0	2.9	2.9	2.8	3.2	2.9	3.0	4.8	2.8
J9eq-9ax		14.6	14.7	14.7	14.6	14.7		14.7	
J9eq-10eq		1.9			1.8	1.6		2.4	1.7
J10q-10x		14.2	14.2	14.7	14.2	14.3	14.2	14.7	14.1
J11-11	11.8	11.8	11.8	11.8	11.8	11.8	11.8	11.9	0
			JAr: 7.8	JAr: 7.5	JAr: 5.1	JAr: 8.4	JAr: 8.4		JThx: 6.9
				JAr: 1.7	JAr: 3.5	JAr: 2.4			
				JAr: 1.2	JAr: 1.2				

[a] For numbering of protons see Fig. 1.

(C-11), 61.3 (C-2), 55.1 (OMe), 54.0 (C-9), 52.4 (C-7), 51.3 (C-10), 47.6 (C-4), 45.2 (C-5), 20.8 (OAc). HRMS calcd for $C_{20}H_{24}O_7SNa$ (M+Na): 431.1140, found: 431.1137.

(+)-Dimethyl (1,1,2-trimethylpropyl)silyl[(1*R*,3*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-methoxy-3-phenyl-7,13-dioxa-10-thiatetracyclo[6.3.1.1$^{1.4}$.0$^{5.12}$]tridec-12-yl]methyl ether (13). $[\alpha]_D^{22}$=+60 (*c* 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 145.5 (Ar), 128.5 (Ar), 127.1 (Ar), 126.4 (Ar),108.1 (C-1), 85.0 (C-3), 83.3 (C-6), 78.9 (C-8), 68.6 (C-11), 61.2 (C-2), 54.6 (OMe), 53.0 (C-7), 49.3 (C-4), 44.5 (C-5), 34.0 (*C*HCH$_3$ Thx), 31.2 (C-10), 29.3 (C-9), 25.1 (Thx), 20.2 (Thx), 18.5 (Thx), −3.5 (Si*C*H$_3$), −3.6 (Si*C*H$_3$). HRMS calcd for $C_{26}H_{40}O_4SSiNa$ (M+Na): 499.2314, found: 499.2319.

(+)-Dimethyl (1,1,2-trimethylpropyl)silyl [(1*R*,4*S*,5*R*,6*S*,*S*,12*S*)-6-methoxy-7,13-dioxa-10-thiatetracyclo[6.3.1.1$^{1.4}$.0$^{5.12}$]-tridec-2-en-12-yl]methyl ether (12). Compound **11** (40.0 mg, 156 μmol) and imidazole (14.5 mg, 213 μmol) were dissolved in DMF (1.0 mL) under argon and dimethylthexylsilyl chloride (50.0 μl, 255 μmol) was added. The reaction mixture was stirred at room temperature for 21 h, poured on to water (20 mL) and extracted with CH_2Cl_2 (4×5 mL). The combined organic phases were washed with water (5 mL) and dried ($MgSO_4$). Flash chromatography (heptane/EtOAc 2:1) gave **11** (43.1 mg, 69%). $[\alpha]_D^{23}$=+86 (*c* 0.58, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 6.51 (dd, 1H, *J*=5.7, 1.8 Hz, H-4), 6.29 (d, 1H, *J*=5.7 Hz, H-5), 5.00 (s, 1H, H-1), 4.96 (d, 1H, *J*=1.8 Hz, H-3), 4.29 (t, 1H, *J*=2.8 Hz, H-8), 3.71 (d, 1H, *J*=10.2 Hz, H-11), 3.55 (d, 1H, *J*=14.1 Hz, H-10ax), 3.50 (d, 1H, *J*=10.2 Hz, H-11), 3.38 (dd, 1H, *J*=14.1, 3.0 Hz, H-9ax), 3.36 (s, 3H, OMe), 2.89 (m, 2H, H-9eq and H-10eq), 1.77 (s, 1H, H-2), 1.65 (septet, 1H, *J*=6.9 Hz, C*H*CH$_3$ Thx), 0.91 (d, 6H, *J*=6.9 Hz, CH*CH*$_3$ Thx), 0.88 (s, 6H, C*CH*$_3$ Thx), 0.11 (s, 6H, Si*CH*$_3$). ^{13}C NMR ($CDCl_3$): δ 139.2, 137.7, 107.4, 85.7, 80.8, 76.9, 70.2, 56.9, 54.8, 54.1, 34.2, 29.1, 25.4, 20.5, 20.4, 18.7, −3.3, −3.4. HRMS calcd for $C_{20}H_{34}O_4SSiNa$ (M+Na): 421.1845, found: 421.1847.

15ab. ^{1}H NMR (**15a**) ($CDCl_3$): δ 7.31–7.19 (m, 5H, Ar), 6.23 (s, 1H, H-1), 4.61 (s, 1H, H-3), 4.42 (t, 1H, *J*=3.0 Hz, H-8), 4.41/4.33 (ABq, 2H, *J*=11.7 Hz, H-11), 3.13 (d, 1H, *J*=14.3 Hz, H-10ax), 3.12 (dd, 1H, *J*=14.7, 3.0 Hz, H-9ax), 3.01 (ddd, 1H, *J*=14.7, 3.0, 1.8 Hz, H-9eq), 2.96 (dd, 1H, *J*=8.5, 6.4 Hz, H-4*endo*), 2.92 (m, 1H, H-10eq), 2.50 (dd, 1H, *J*=13.1, 8.5 Hz, H-5*exo*), 2.34 (s, 1H, H-2), 2.15 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.49 (dd, 1H, *J*=13.1, 6.3 Hz, H-5*exo*). ^{1}H NMR (**15b**) ($CDCl_3$): δ 6.29 (s, 1H, H-1), 4.82 (d, 1H, *J*=5.2 Hz, H-3). ^{13}C NMR ($CDCl_3$): δ 170.3, 169.9, 144.7, 128.7, 127.0, 126.7, 101.9, 84.8, 83.2, 79.9, 68.2, 61.6, 51.4, 48.9, 44.7, 30.9, 28.6, 21.2, 20.8. HRMS calcd for $C_{21}H_{24}O_6SNa$ (M+Na): 427.1191, found: 427.1199.

16ab. ^{1}H NMR (**16a**) ($CDCl_3$): δ 7.10 (m, 2H, Ar), 6.74 (m, 2H, Ar), 6.22 (s, 1H, H-1), 5.23 (br s, 1H, OH), 4.53 (s, 1H, H-3), 4.41 (m, 1H, H-8), 4.39/4.32 (ABq, 2H, *J*=11.7 Hz, H-11), 3.12 (m, 2H, H-9ax,10ax), 3.01 (m, 1H, H-9eq), 2.91 (m, 1H, H-10eq), 2.89 (m, 1H, H-4*endo*), 2.46 (dd, 1H, *J*=13.0, 8.5 Hz, H-5*endo*), 2.32 (s, 1H, H-2), 2.14 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.43 (dd, 1H, *J*=13.0, 6.3 Hz, H-5*exo*). ^{1}H NMR (**16b**) ($CDCl_3$): δ 6.28 (s, 1H, H-1), 4.79 (m, 1H, H-3), 2.54 (d, 1H, *J*=15.0 Hz, H-10), 2.26 (s, 1H, H-2), 2.21 (d, 1H, *J*=15.0 Hz, H-10). ^{13}C NMR ($CDCl_3$): δ 170.4, 170.0, 154.4, 136.9, 128.1, 116.5, 115.4, 101.9, 84.9, 83.1, 79.9, 68.2, 61.6, 51.4, 51.3, 48.1, 44.7, 30.9, 28.6, 21.2, 20.9. HRMS calcd for $C_{21}H_{24}O_7SNa$ (M+Na) 443.1140, found 443.1136.

[(1*R*,3*R*,4*S*,5*R*,6*R*,8*S*,12*S*)-6-Methylcarbonyloxy-3-(4-methyl benzoic ester)-7,13-dioxa-10-thiatetracyclo-[6.3.1.1$^{1.4}$.0$^{5.12}$]tridec-12-yl]methyl acetate (17). $[\alpha]_D^{22}$=+60.0 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.94 (m, 2H, Ar), 7.33 (m, 2H, Ar), 6.22 (s, 1H, H-1), 4.61 (s, 1H, H-3), 4.42 (t, 1H, H-8), 4.40/4.32 (ABq, 2H, H-11), 3.89 (s, 3H, OMe), 3.13 (d, 1H, *J*=14.3 Hz, H-10ax), 3.12 (dd, 1H, *J*=14.8, 8.5 Hz, H-9ax), 3.02 (dd, 1H, *J*=8.5, 6.3 Hz, H-4*endo*), 3.00 (m, 1H, H-9eq), 2.92 (d, 1H, *J*=14.3 Hz, H-10eq), 2.52 (dd, 1H, *J*=13.1, 8.5 Hz, H-5*endo*), 2.35 (s, 1H, H-2), 2.14 (s, 3H, OAc), 2.04 (s, 3H, OAc), 1.47 (dd, 1H, *J*=13.1, 6.3 Hz, H-5*exo*). ^{13}C NMR ($CDCl_3$): δ 170.2, 169.8, 166.8, 149.7, 130.0, 128.7, 127.0, 101.8, 84.5, 83.4, 79.9, 68.0, 61.6, 52.0, 51.4, 48.9, 44.5, 30.8, 28.6, 21.2, 20.8. HRMS calcd for $C_{23}H_{26}O_8SNa$ (M+Na) 485.1246, found 485.1245.

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