Tetrahedron Letters 49 (2008) 7403–7405

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Ring-closing metathesis for the synthesis of novel 9- and 10-membered silicon-containing benzo-fused heterocycles

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ARTICLE INFO

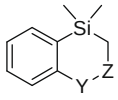
Article history:
Received 8 September 2008
Revised 6 October 2008
Accepted 14 October 2008
Available online 18 October 2008

ABSTRACT

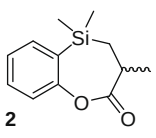
A ring-closing metathesis (RCM) strategy afforded a number of novel 9- and 10-membered benzo-fused compounds containing at least one silicon atom as part of the heterocyclic portion. In this manner, the following compounds containing heterocyclic rings of 9–10 atoms were synthesized: (*Z*)-2,2-dimethyl-7-[(4-methylphenyl)sulfonyl]-2,3,6,7-tetrahydrobenzo[*h*][1,7,2]oxazasilonine, (*Z*)-2,2-dimethyl-3,6-dihydro-2*H*-benzo[*h*][1,7,2]dioxasilonine, (*Z*)-8-isopropoxy-9-methoxy-3,3-dimethyl-1,3,4,7-tetrahydrobenzo[*g*]-[1,2]oxasilonine and (*Z*)-2,2,7,7-tetramethyl-2,3,6,7-tetrahydrobenzo[*i*][1,8,2,7]dioxadisilecine.

Medicinal chemistry regularly makes use of benzo-fused compounds as templates for the investigation of pharmaceutical scaffolds.[1] In addition, the use of silicon as an isostere in drug discovery has also been seen to increase;[2] this would make benz-annulated compounds containing silicon atoms in their backbone interesting candidates for biological evaluation. Over the past few decades, benzo-fused heterocycles containing silicon in the heterocyclic portion of the molecule have seen sporadic investigation.[3] Examples include compounds which comprise 6,6-, 6,7- and 6,8-fused systems, such as the generalized structures **1a**,[4] **1b**,[5] **1c**,[6] benzoxasilepin-2(3*H*)-one **2**[7] and benzazasilocine **3**,[8] respectively (Fig. 1).

Rather surprisingly, although ring-closing metathesis (RCM) has seen a tremendous increase in synthetic applications over the last decade,[9] very few examples resulting in the synthesis of compounds such as those represented in Figure 1 have been reported.[10] To the best of our knowledge only Rodríguez-García and co-workers have been active in this area, in their elegant pursuit of the pterocarpans and related compounds.[11] Amongst other examples, this group demonstrated that the application of RCM to compounds **5** and **8**, synthesized from substrates **4** and **7**, readily afforded 2,3-dihydro-1,2-benzoxasilepine **6** and 3,6-dihydro-2*H*-1,2-benzoxasilocine **9**, respectively (Scheme 1).



1a Y = SO_2 or CO, Z = NH
1b Y = NMe, NEt or NBn, Z = CH_2
1c Y = CH_2, Z = NMe, NEt or NBn



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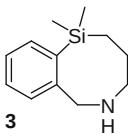

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Figure 1. Examples of previously prepared dimethylsilyl-containing bicyclic benzo-fused compounds.

Our research group has been heavily involved in the application of RCM to the synthesis of benzo-fused bicyclic molecules.[12] It was thus decided to investigate the application of metathesis and isomerization-metathesis strategies towards the synthesis of other silicon-containing benzo-fused heterocycles. This communication describes the successes of our investigations as well as some of the limitations of this approach.

In the first experimental work performed, it was decided to repeat the work described by Rodríguez-García and co-workers (Scheme 1),[11] with the difference that the second-generation Grubbs' catalyst **11** was used in preference to **10**.[13] The reason for this was because one of the goals of this research was to extend the methodology to other potentially electron-rich substrates.

The initial results were very promising, and it was thus decided to investigate the RCM reaction for the formation of other annulated heteroatom-containing silacycles, the first of which contained nitrogen and oxygen atoms. To this end, substituted phenol **13**[14] was silylated with reagent **12**[15] to afford the diallyl species **14** in a good yield of 80% (Scheme 2). A RCM reaction with catalyst **11** proved to be a straightforward process and afforded the 9-membered benzoxazasilonine **15** in good yield (78%).[16]

Rodríguez-García and co-workers successfully employed an 'isomerization-RCM' strategy to obtain compounds with the skeleton **9**. It was thus decided to investigate whether it was possible to utilize a similar strategy involving an *O*-vinyl ether obtained from

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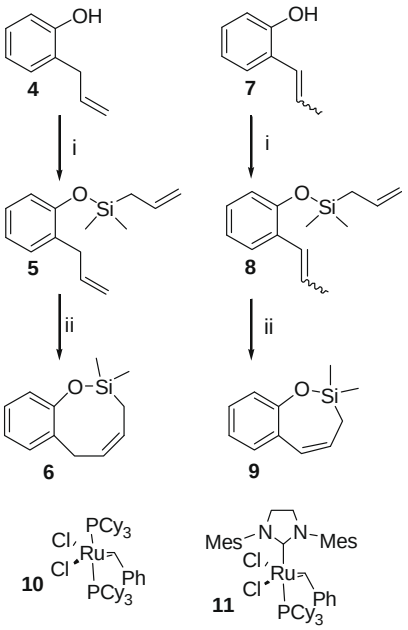
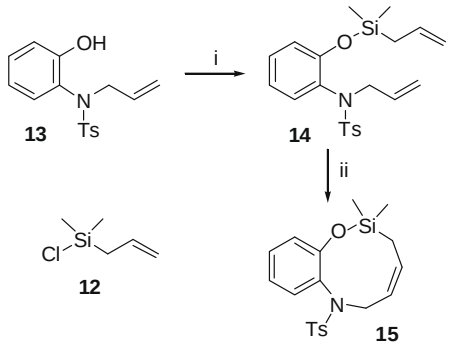
doi:10.1016/j.tetlet.2008.10.067



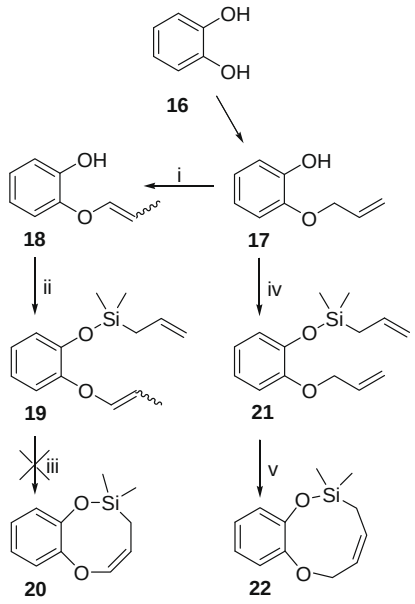
Scheme 1. Rodríguez-García's work.[11] Reagents and conditions: (i) Et_3N, CH_2Cl_2, allylchlorodimethylsilane **12**; (ii) 5% catalyst **10**.



Scheme 2. Reagents and conditions: (i) Et_3N, CH_2Cl_2, allylchlorodimethylsilane **12**, 0 °C–rt, N_2, 15 h, 80%; (ii) 5% catalyst **11**, CH_2Cl_2, rt, N_2, 12 h, 78%.

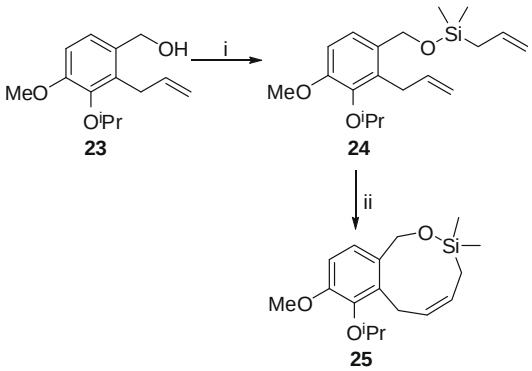
the corresponding *O*-allyl ether.[17,18] Catechol **16** was thus mono-allylated to afford compound **17** (Scheme 3). Subsequent treatment of this substance with the ruthenium hydride complex [RuClH-(CO)$(PPh_3)_3$][19] successfully afforded the vinyl ether **18**, as a mixture of *E*/*Z* isomers. Conversion into compound **19** with allylchlorodimethylsilane **12** then occurred without problem. However, we were unable to initiate the metathesis reaction to afford the 8-membered heterocycle **20**, a benzodioxasilocine, and are unable to offer a rationalization for this result as our previous experience with the RCM of similar propenyl ethers has been excellent.[18] Unfortunately, even under harsher conditions, only the unreacted starting material was obtained after chromatography. However, a RCM strategy utilizing the unisomerized scaffold **17** gave more promising results: treatment of the allyl ether **17** with **12** afforded the bis-allyl product **21** in good yield (Scheme 3). This compound then underwent cyclization in the presence of catalyst **11**, producing the benzodioxasilonine **22**,[20] albeit only in a low, unoptimized 22% yield.

A search for other potential scaffolds for the RCM identified the substituted benzyl alcohol **23**, a substrate utilized previously in our studies.[21] This compound was readily converted into silylated compound **24** in a yield of 85% (Scheme 4). Application of the

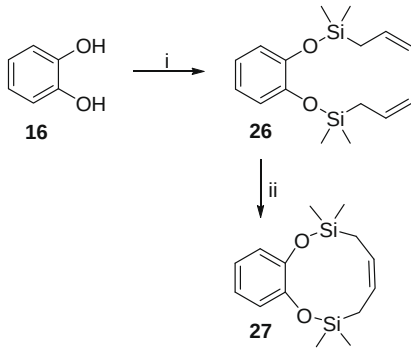


Scheme 3. Reagents and conditions: (i) 3% catalyst [RuClH(CO)$(PPh_3)_3$], CH_2Cl_2, reflux, N_2, 20 h, 56%; (ii) Et_3N, CH_2Cl_2, allylchlorodimethylsilane **12**, rt, N_2, 5 h, 73%; (iii) 5% catalyst **11**, CH_2Cl_2, reflux, N_2, 24 h; (iv) Et_3N, CH_2Cl_2, allylchlorodimethylsilane **12**, rt, N_2, 66 h, 76%; (v) 5% catalyst **11**, CH_2Cl_2, reflux, N_2, 18 h, 22%.

metathesis methodology then gratifyingly afforded (*Z*)-8-isopropoxy-9-methoxy-3,3-dimethyl-1,3,4,7-tetrahydrobenzo[*g*][1,2]-oxasilonine **25**[22] in a good yield of 82%.



Scheme 4. Reagents and conditions: (i) Et_3N, CH_2Cl_2, allylchlorodimethylsilane **12**, rt, N_2, 40 h, 85%; (ii) 5% catalyst **11**, CH_2Cl_2, reflux, N_2, 8 h, 82%.



Scheme 5. Reagents and conditions: (i) Et_3N, CH_2Cl_2, allylchlorodimethylsilane **12**, rt, N_2, 66 h, 76%; (ii) 5% catalyst **11**, CH_2Cl_2, reflux, N_2, 18 h, 96%.

Finally, we investigated whether larger benzo-fused ring-systems containing silicon could also be synthesized utilizing the RCM strategy. Catechol **16** was thus treated with allylchlorodimethylsilane **12**, and the disilylated compound **26** was isolated after chromatography in good yield (Scheme 5). Subsequent reaction of **26** with catalyst **11** then gave compound **27**.[23] Product **27** contains a 10-membered benzo-fused ring, a system that traditionally is challenging to synthesize by way of a metathesis strategy.[15a]

We have thus shown that the versatile RCM reaction with Grubbs' second-generation catalyst **11** can be applied to the synthesis of a number of silicon-containing benzo-fused heterocycles. The extension of this work to the synthesis of other interesting systems is currently under investigation, and will be reported in due course.

Acknowledgements

This work was supported by the National Research Foundation (NRF, GUN 2053652), Pretoria, and the University of the Witwatersrand (University and Science Faculty Research Committees). Mr. S. Mthembu and Mr. T. Tshabalala are thanked for initial repetition of the Rodríguez-García work. Professor C. B. de Koning is thanked for helpful discussions. Dr. R. Ul Islam gratefully acknowledges the Poliomyelitis Research Foundation, South Africa for financial support. Messrs R. Mampa (NMR), T. van der Merwe (MS), M. Brits (MS) and Dr. A. Dinsmore (MS) are also thanked for providing the spectroscopic services.

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16. *(Z)-2,2-Dimethyl-7-[(4-methylphenyl)sulfonyl]-2,3,6,7-tetrahydrobenzo[h][1,7,2]-oxazasilonine* **15**: Benzenesulfonamide **14** (0.10 g, 0.25 mmol) was dissolved in CH_2Cl_2 under N_2 and catalyst **11** (0.011 g, 0.013 mmol, 5 mol %) was added. The reaction mixture was stirred at rt for 12 h. After evaporation of the solvent, the residue was subjected to column chromatography (8% EtOAc/hexane) to yield the pure ring-closed product **15** (0.072 g, 78%). Mp: 75–77 °C; ν_{max} (thin film/cm^{-1}): 1596, 1487, 1465; ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.61 (d, 2H, J = 8.2 Hz, 2 × ArH), 7.26 (d, 2H, J = 8.2 Hz, 2 × ArH), 7.16–7.11 (m, 1H, ArH), 6.91–6.76 (m, 3H, 3 × ArH), 5.72–5.63 (m, 1H, NCH_2CH=CH), 5.08–5.00 (m, 1H, CH=$CHCH_2Si$), 4.13 (br d, 2H, J = 4.5 Hz, NCH_2), 2.42 (s, 3H, $ArCH_3$), 1.77 (br s, 2H, $SiCH_2$), 0.22 [s, 6H, $Si(CH_3)_2$]; ^{13}C NMR (75 MHz; $CDCl_3$, assignments with same superscript may be interchanged): δ 154.1 (C), 143.1 (C), 135.4 (C), 132.1 (CH), 130.2 (C), 129.6 (CH), 129.2 (2 × CH), 128.9 (CH), 128.0 (2 × CH), 122.0 (CH), 121.8 (CH), 120.2 (CH), 46.9 (NCH_2), 21.5 ($ArCH_3$),[a] 20.6 ($SiCH_2$),[a] −1.4 [$Si(CH_3)_2$]; m/z (EI): 373 (M^+, 0.34%), 319 (72), 218 (21), 203 (22), 202 (16), 164 (100), 91 (12); HRMS: Calculated for $C_{19}H_{23}NO_3SSi$: 373.1168, found: 373.1162.
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20. *(Z)-2,2-Dimethyl-3,6-dihydro-2H-benzo[h][1,7,2]dioxasilonine* **22**: ν_{max} (thin film/cm^{-1}): 2927, 1639, 1495, 1249; ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.75–6.62 (m, 1H, ArH), 6.60–6.42 (m, 3H, 3 × ArH), 5.64–5.50 (m, 1H, *HC*=CH), 5.20–5.06 (m, 1H, HC=C*H*), 4.43–4.35 (m, 2H, CH_2O), 1.58–1.44 (m, 2H, CH_2Si), −0.05 [br s, 6H, $Si(CH_3)_2$]; ^{13}C NMR (75 MHz; $CDCl_3$): δ 148.9 (C), 147.4 (C), 133.5 (CH), 123.3 (CH), 122.1 (CH), 121.8 (CH), 121.5 (CH), 119.6 (CH), 68.6 (CH_2), 21.4 (CH_2), −0.5 [$Si(CH_3)_2$]; m/z (EI): 221 (M^++H, 12%), 205 (5), 170 (10), 169 (64), 166 (100), 151 (56), 136 (30), 108 (2), 77 (3), 63 (4); HRMS: Calculated for $C_{12}H_{16}O_2Si$: 220.0920, found: 220.0914.
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22. *(Z)-8-Isopropoxy-9-methoxy-3,3-dimethyl-1,3,4,7-tetrahydrobenzo[g][1,2]oxasilonine* **25**: ν_{max} (thin film/cm^{-1}): 1601, 1487, 1435, 1270, 1195; ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.94 (d, 1H, J = 8.3 Hz, ArH), 6.72 (d, 1H, J = 8.3 Hz, ArH), 5.59–5.43 (m, 2H, *HC*=C*H*), 4.73 (s, 2H, $ArCH_2OSi$), 4.61–4.52 [m, 1H, $CH(CH_3)_2$], 3.85 (s, 3H, OCH_3), 3.59 (br d, 2H, J = 7.2 Hz, $ArCH_2CH$), 1.76 (br d, 2H, J = 7.8 Hz, CH_2Si), 1.31 [d, 6H, J = 6.2 Hz, $CH(CH_3)_2$], 0.19 [s, 6H, $Si(CH_3)_2$]; ^{13}C NMR (75 MHz; $CDCl_3$): δ 152.8 (C), 145.2 (C), 134.3 (C), 131.1 (C), 126.2 (CH), 125.5 (CH), 123.0 (CH), 109.5 (CH), 74.3 (CH), 64.5 (CH_2), 55.5 (OCH_3), 25.4 (CH_2), 22.4 (2 × CH_3), 17.8 (CH_2), −1.67 [$Si(CH_3)_2$]. m/z (EI): 307 (M+H$^+$, <1%), 177 (100), 145 (40), 117 (46), 115 (82), 91 (38), 55 (36); HRMS: Calculated for $C_{17}H_{27}O_3Si$ (M+H$^+$): 307.1729, found: 307.1723.
23. *(Z)-2,2,7,7-Tetramethyl-2,3,6,7-tetrahydrobenzo[i][1,8,2,7]dioxadisilecine* **27**: ν_{max} (thin film/cm^{-1}): 1631, 1499, 1451, 1252, 1158, 1107; ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.57 (br s, 4H, 4 × ArH), 5.25 (br t, 2H, J = 5.9 Hz, 2 × =CH), 1.48–1.51 (m, 4H, 2 × CH_2), −0.04 [s, 12H, 2 × $Si(CH_3)_2$]; ^{13}C NMR (75 MHz; $CDCl_3$): δ 146.7 (2 × C), 122.6 (2 × CH), 122.0 (2 × CH), 121.0 (2 × CH), 19.4 (2 × CH_2), −1.2 [2 × $Si(CH_3)_2$]; m/z (EI): 279 (M+H$^+$, 24%), 263 (6), 227 (3), 181 (2), 169 (8), 167 (14), 166 (100), 151 (4), 136 (3), 98 (22), 95 (11), 69 (2); HRMS: Calculated for $C_{14}H_{22}O_2Si_2$: 278.1158, found: 278.1153.