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Synthesis of 2,5-dihydrobenzo[*b*]oxepines and 5,6-dihydro-2*H*-benzo[*b*]oxocines based on a '[3+3] cyclization-olefin-metathesis' strategy

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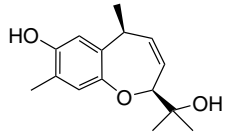
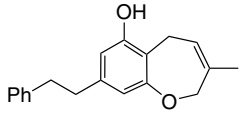
Abstract—Functionalized 2,5-dihydrobenzo[*b*]oxepines and 5,6-dihydro-2*H*-benzo[*b*]oxocines were prepared based on a '[3+3] cyclization-olefin-metathesis' strategy.

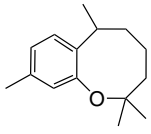
2,3,4,5-Tetrahydrobenzo[*b*]oxepines are of pharmacological relevance and occur in a number of natural products, such as heliannuol C and D[1] or plumbagic acid lactone.[2] Their eight-membered ring analogs, 3,4,5,6-tetrahydro-2*H*-benzo[*b*]oxocines, are found, for example, in heliannuol A and K,[1,3] helianane,[4] and protosappanine B.[5] 2,5-Dihydrobenzo[*b*]oxepines are present, for example, in heliannuol B[1] and in the radulanins A, H, and L isolated from *Haliclona fascigera* and *Radula variabilis*, respectively.[6] The 5,6-dihydro-2*H*-benzo[*b*]oxocine core structure occurs, for example, in heliannuol G and H,[4] specionine,[7] and sophoroside A.[7] Some years ago, Snieckus and co-worker reported the synthesis of benzene-fused oxygen heterocycles by application of a 'directed-ortho-metalation (DoM)-olefin-metathesis' strategy.[8] In recent years, a number of natural product syntheses based on RCM have been reported.[9] Herein, we report a new and convenient synthesis of 2,5-dihydrobenzo[*b*]oxepines and 5,6-dihydro-2*H*-benzo[*b*]-oxocines based on a '[3+3] cyclization-olefin-metathesis' strategy. Our approach relies on the regioselective assembly of the benzene moiety by [3+3] cyclizations of 1,3-bis(trimethylsilyloxy)hepta-1,3,6-trienes and 1,3-bis(trimethylsilyloxy)octa-1,3,7-trienes with 3-silyloxyalk-2-en-1-ones to give functionalized salicylates.[10,11] The latter were transformed into the desired products by O-allylation and subsequent ring-closing metathesis (RCM).



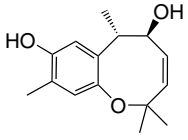
Heliannuol B



Radulanin A



Helianane



Heliannuol H

The 1,3-bis-silyl enol ethers **5a**,**b** were prepared according to a known procedure (Scheme 1).[12,13] The $TiCl_4$ mediated [3+3] cyclization of **5a** with 1,1,3,3-tetramethoxypropane afforded the allyl-substituted salicylate **6a** (Table 1). Allylation of the hydroxy group afforded the allylic ether **7a**, which was transformed into the desired 2,5-dihydrobenzo[*b*]oxepine **8a** by RCM using Grubbs' catalyst **9**.[14–16] Likewise, the 5,6-dihydro-2*H*-benzo[*b*]oxocine **8b** was prepared from 1,3-bis-silyl enol ether **5b**. Application of the Mitsunobu reaction for O-allylation was not successful.

Keywords: Cyclizations; Heterocycles; Medium-sized rings; Ring-closing metathesis; Silyl enol ethers.
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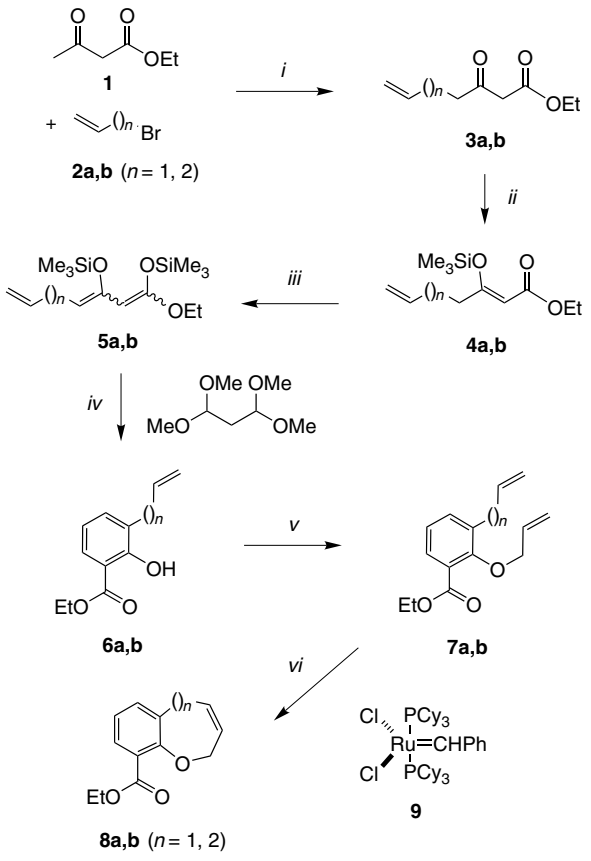


Scheme 1. Synthesis of **8a**,**b**. Reagents and conditions: (i) (1) LDA (2.3 equiv), THF, 0 °C, 1 h, (2) **2a**,**b**, −78 → 20 °C; (ii) Me_3SiCl, NEt_3, toluene, 20 °C, 24 h; (iii) (1) LDA, THF, −78 °C, 1 h, (2) Me_3SiCl, 20 °C, −78 → 20 °C; (iv) $TiCl_4$, CH_2Cl_2, −78 → 20 °C; (v) $H_2C{=}CH{-}CH_2Br$ (1.5 equiv), NaH (2.0 equiv), TBAI (2.0 equiv), THF, 0 °C, 24 h, 0 → 20 °C, 8–12 h; (vi) **9** (5 mol %), CH_2Cl_2 (1.5 equiv), 20 °C, 6–8 h.

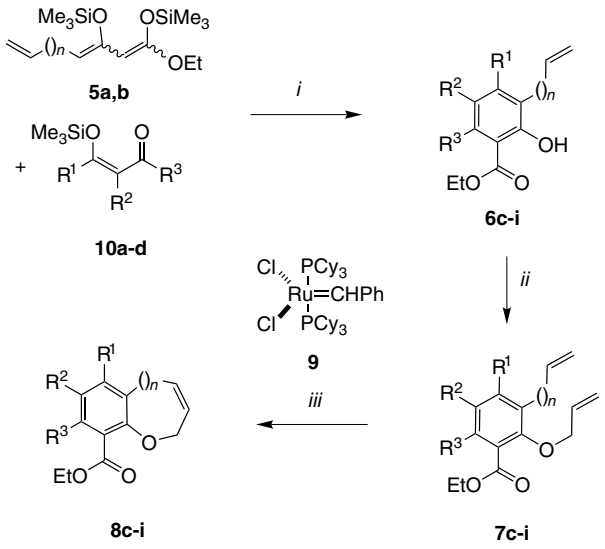
Table 1. Products and yields

6–8	*n*	% (**6**)[a]	% (**7**)[a]	% (**8**)[a]
a	1	45	86	99
b	2	53	84	75

[a] Yields of isolated products.

The $TiCl_4$ mediated [3+3] cyclization of **5a** with silyl enol ethers **10a**–**c**, prepared from pentane-2,4-dione, 3-methylpentane-2,4-dione, and heptane-3,5-dione, afforded the allyl-substituted salicylates **6c**–**e**, which were transformed into the 2,5-dihydrobenzo[*b*]oxepines **8c**–**e** (Scheme 2 and Table 2). The tetracyclic 2,5-dihydrobenzo[*b*]oxepine **8f** was prepared from **10d**, which is available from 2-acetyltetralone. The 5,6-dihydro-2*H*-benzo[*b*]oxocines **8g**–**i** were prepared from 1,3-bis-silyl enol ether **5b**.

The [3+3] cyclizations (to give salicylates **6a**–**i**) proceeded in 31–52% yield; the yields are similar to those reported for related cyclizations[11] and are not decreased by the presence of the additional alkenyl moiety in the 1,3-bis-silyl enol ether. Migration of the olefin functionality (to form cyclic enol ethers) was *not* observed during the ring-closing metathesis step.[17] The



Scheme 2. Synthesis of **8c**–**i**. Reagents and conditions: (i) $TiCl_4$ (1.0 equiv), CH_2Cl_2, −78 → 20 °C; (ii) $H_2C{=}CH{-}CH_2Br$ (1.5 equiv), NaH (2.0 equiv), TBAI (2.0 equiv), THF, 0 → 20 °C, 8–12 h; (iii) **9** (5 mol %), CH_2Cl_2 (1.5 equiv), 20 °C, 6–8 h.

Table 2. Products and yields

6–8	*n*	R^1	R^2	R^3	% (**6**)[a]	% (**7**)[a]	% (**8**)[a]
c	1	Me	H	Me	44	85	90
d	1	Me	Me	Me	52	95	93
e	1	Et	H	Et	31	78	91
f	1	$C_6H_4(CH_2)_2$		Me	43	77	80
g	2	Me	Me	Me	47	76	76
h	2	Et	H	Et	50	82	91
i	2	$C_6H_4(CH_2)_2$		Me	33	96	70

[a] Yields of isolated products.

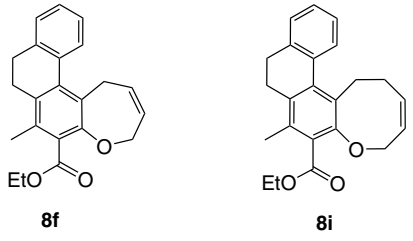


Figure 1.

structures of tetracyclic 2,5-dihydrobenzo[*b*]oxepine **8f** and 5,6-dihydro-2*H*-benzo[*b*]oxocine **8i** are given below for clarity (Fig. 1).

In summary, we have reported a new regioselective synthesis of functionalized 2,5-dihydrobenzo[*b*]oxepines and 5,6-dihydro-2*H*-benzo[*b*]oxocines based on a '[3+3] cyclization-ring-closing-metathesis' strategy.

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