Enantioselective assembly of the benzo[*d*]xanthene tetracyclic core of anti-influenza active natural products†‡

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A combination of an enantioselective conjugate addition/trapping sequence and a ruthenium(III)-catalyzed domino cyclization provides a concise access to benzo[*d*]xanthenes found in several anti-influenza active sesquiterpene natural products.

Emerging resistance to anti-influenza agents in combination with the recent global pandemics are a severe threat. Therefore the search for alternative treatments is an important task. A small class of sesquiterpene natural products that possess promising activity against the influenza A virus has been reported. Stachyflin,[1] the most potent congener displays an IC_{50} value of 3 nM against influenza A virus strains and has been shown to act as a fusion inhibitor.[2] Other members of this family like podosporin,[3] aureol[4] and strongylin[5] are anti-virally active as well. The common structural feature of this compound family is their tetracyclic benzo[*d*]xanthene scaffold **1**, thus making it an attractive target that warrants further attention (Fig. 1).

To explore the potential of this compound class we required a flexible and efficient route to access skeleton **1**. Our retrosynthetic strategy is based on a transition-metal catalyzed domino cyclization of diene **3** (Scheme 1). First, the *C*-ring should be closed *via* a *trans*-selective alkoxy-metalation forming **2**. Subsequently, an addition across the double bond should then build the *A*-ring. A proto-demetalation or a reductive elimination would lead either to the saturated or unsaturated version of **1**. The required precursor **3** derives from ketone **4**, which should be ultimately accessible from enone **5** by an enantioselective conjugate addition/electrophilic trapping sequence.

For the initial enantioselective conjugate addition reaction we employed conditions developed by Alexakis and coworkers forming aluminium enolate **6** with an *ee*-value of 90% (Table 1).[6] However, aluminium enolates are well known for their notorious poor reactivity, impeding most direct electrophilic trapping reactions. Therefore, some optimization was required for an effective one pot addition–alkylation sequence. The reactivity of aluminium enolates is greatly enhanced by their conversion into the corresponding the ate-complex with methyl lithium[7] and further by addition of highly polar solvent additives. HMPA proved to be essential and alternatives like DMPU were not viable

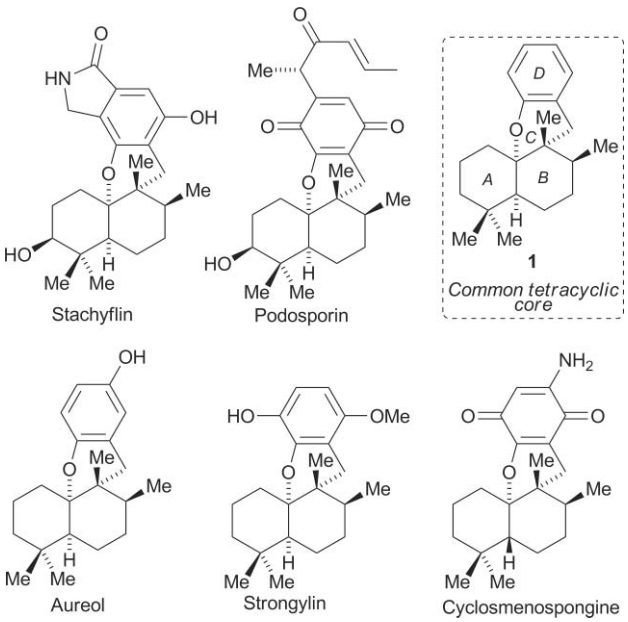
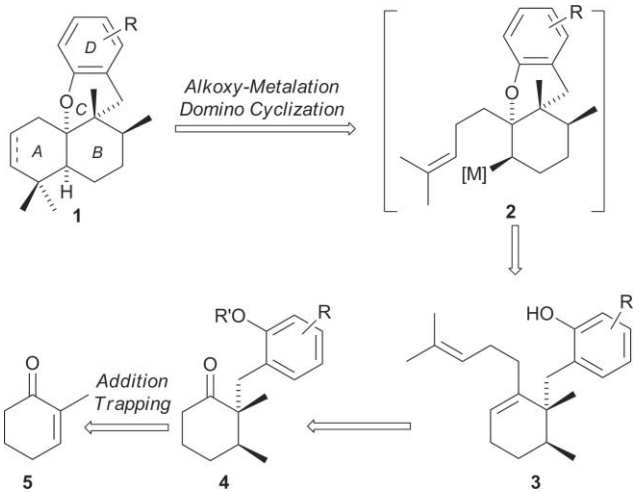


Fig. 1 Benzo[*d*]xanthene sesquiterpene natural products.



Scheme 1 Synthetic strategy for the benzo[*d*]xanthene skeleton.

(Entries 2 and 3). The enolate trapping proceeds well for benzylic and propargylic iodides, while the corresponding bromides are unreactive (Entry 4). The obtained diastereoselectivities range from 6 : 1 to 10 : 1 in favor of the depicted isomer **4**. Remarkably, the alkylation works equally well for sterically demanding *ortho*-disubstituted benzyl iodides and provides **4d** in 63% yield (Entry 7). Less reactive electrophiles *e.g.* 2,6-dichlorobenzyl iodide can be

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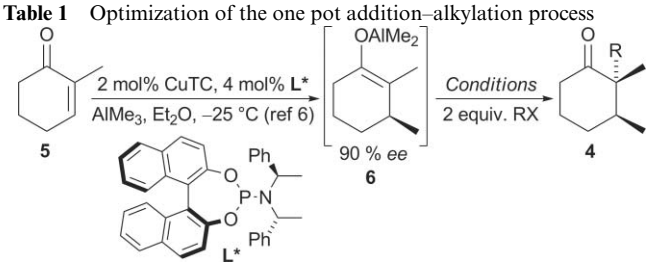
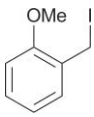
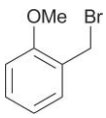
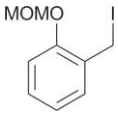
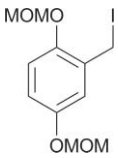
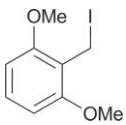
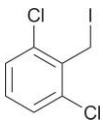
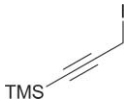
Table 1 Optimization of the one pot addition–alkylation process

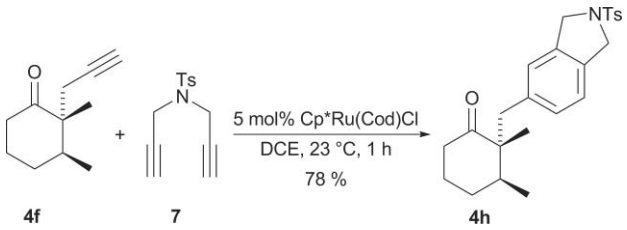


Entry	Conditions	RX	Ketone **4**	Yield [%][a]
1	HMPA		**4a**	< 5
2	MeLi, HMPA		**4a**	67
3	MeLi, DMPU		**4a**	5
4	MeLi, HMPA		**4a**	< 5
5	MeLi, HMPA		**4b**	80
6	MeLi, HMPA		**4c**	78
7	MeLi, HMPA		**4d**	63
8[b]	MeLi, HMPA		**4e**	33
9	MeLi, HMPA		**4f**	61
10	MeLi, HMPA		**4g**	69

[a] Yield of isolated the diastereomer **4**. [b] 48% of 2,3-dimethyl cyclohexanone was isolated additionally.

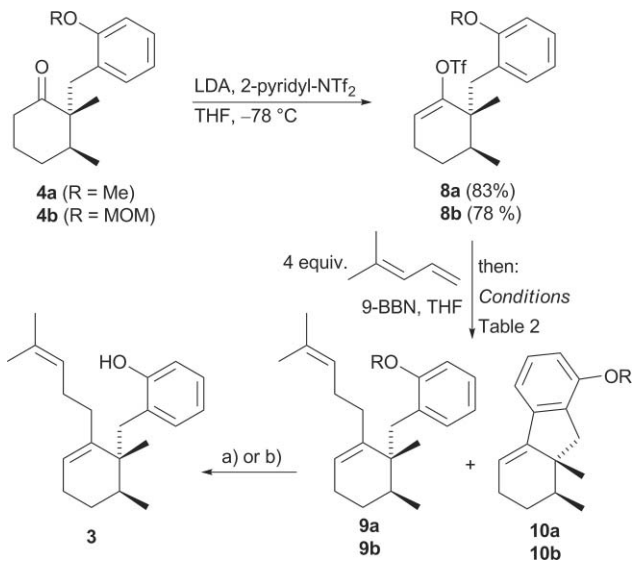
used, although **4e** is obtained in diminished yield along with 2,3-dimethyl ketone (Entry 8).

A ruthenium(II)-catalyzed [2+2+2]-cyclotrimerization reaction with the propargyl substituted ketone **4f** and the tethered diyne **7** can be used to access higher substituted derivatives, *e.g.* **4h** for a synthetic approach to stachyflin congeners (Scheme 2).[8]



Scheme 2 [2+2+2]-Cyclotrimerization opens access to higher substituted derivatives.

Ketones **4a** and **4b** were converted into the vinyl triflates **8a** and **8b** (Scheme 3). The subsequent sp^2–sp^3 cross-coupling reaction required some investigation. Although iron-catalyzed cross-coupling reactions using vinyl triflates and alkyl Grignard-reagents are well precedented for related systems,[9] only traces of desired product **9** were obtained with this specific substrate pair. We attribute this to the hindered neopentylic nature of the vinyl triflate and the moderate stability of the Grignard-reagent. A palladium-catalyzed Suzuki-coupling using the alkyl boron reagent generated *in situ* from 4-methyl pentadiene and 9-BBN was delicate as well (Table 2). The classical conditions for this substrate class, yielded, irrespective of the phosphine ligand employed, predominantly tricyclic product **10** arising from a direct arylation *via* a concerted deprotonation metalation mechanism (Entries 1–3).[10] Replacing the phosphine ligand by its higher homolog triphenylarsine, completely suppressed this reactivity and gave rise to the desired cross-coupled product **9** in almost quantitative yield. Removal of the phenolic protecting group proceeded either under acidic conditions for R = MOM, or using lithium *n*-butylthiolate in HMPA for R = Me giving phenol **3** in 40% and 81% yield, respectively.



Scheme 3 Synthesis of intermediate **3**, *Reagents and conditions*: a) (R = Me): 2 equiv. *n*BuSLi, HMPA, 100 °C, 2 h, 81%; b) (R = MOM): 1 M HCl, MeOH, 23 °C, 12 h, 41%.

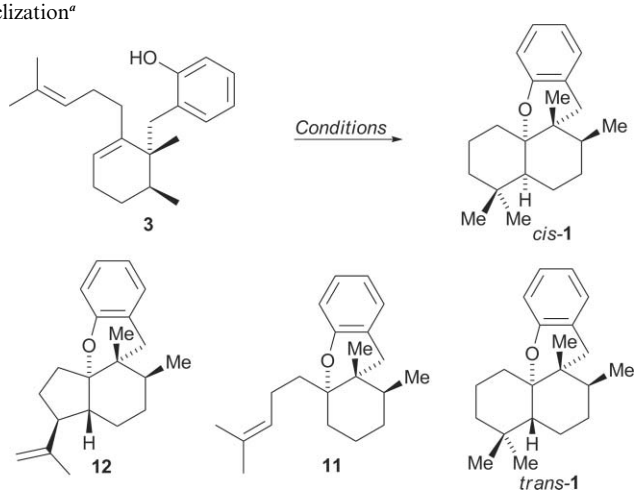
With the free phenol **3**, we then explored different metals and conditions for the anticipated cascade cyclization (Table 3). Classical *trans*-nucleo-palladation selective Wacker-type conditions using palladium(II)-complexes[11] resulted mainly in the slow

Table 2 sp^2–sp^3 Cross-coupling *vs.* direct arylation

Entry	Conditions	**9**[a]	**10**[a]
1	5% $PdCl_2$(dppf), K_3PO_4, THF, 65 °C	< 5%(**9a**)	72%(**10a**)
2	5% $Pd(OAc)_2$, 10% SPhos, K_3PO_4, THF, H_2O, 55 °C	21%(**9a**)	63%(**10a**)
3	5% $Pd(PPh_3)_4$, CsF, dioxane, 85 °C	< 5%(**9a**)	91%(**10a**)
4	5% $Pd(dba)_2$, 12% $AsPh_3$, K_3PO_4, DMF, H_2O, 55 °C	98%(**9a**)	0%(**10a**)
5	5% $Pd(dba)_2$, 12% $AsPh_3$, K_3PO_4, DMF, H_2O, 55 °C	99%(**9b**)	0%(**10b**)

[a] Isolated yields.

Table 3 Exploration of the cascade cyclization[a]



Entry	Conditions	*cis*-**1**[b]	*trans*-**1**[b]	**11**[b]	**12**[b]
1	20% $PdCl_2(CH_3CN)_2$, LiCl, Na_2CO_3, BQ, THF, 60 °C, 48 h	—	—	—	69%
2[c]	10% Pd(hfacac)$_2$, Na_2CO_3, BQ, THF, 60 °C, 48 h	—	—	—	5%
3	10% $PtCl_2$, CH_3NO_2, 45 °C, 3 h	—	9%	41%	—
4	10% $PtCl_4$, CH_2Cl_2, 23 °C, 1 h	—	< 5%	54%	—
5[c]	10% $AgNTf_2$, CH_3CN, 40 °C, 24 h	—	—	< 5%	—
6	20% $RuCl_3$, 60% AgOTf, 40% PPh_3, 50% $Cu(OTf)_2$, CH_3CN, 80 °C, 5 h	< 5%	69%	9%	—
7	20% Cp*$RuCl_2$, 40% AgOTf, 20% PPh_3, 50% $Cu(OTf)_2$, CH_3CN, 80 °C, 2 h	—	11%	38%	—
8[c]	10% TFA, CH_3CN, 23 °C, 18 h	—	—	—	—
9	10% TfOH, toluene, 80 °C, 10 min	—	< 5%	< 5%	—
10	10% TfOH, $MeNO_2$, 23 °C, 18 h	—	20%	—	—

[a] Reaction conditions: 14.9 mg (0.05 mmol) **3**, 0.05 M in the indicated solvent; [b] Yields of isolated products; [c] Starting material **3** was recovered.

formation of product **12** arising from a preferred 5-*exo*-*trig* ring closure of the *A*-ring (Entries 1–2). Platinum(II) as well as platinum(IV) complexes exhibited good reactivity towards the first cyclization,[12] but were not competent for a ring closure of the second carbacycle, thus yielding the tricyclic hydroalkoxylation product **11** (Entries 3–4). Cationic silver(I) complexes were much less reactive (Entry 5). The condition reported by Ohta and coworkers using cationic ruthenium(III) complexes for the formation of dihydrobenzofurans from 2-allylphenols,[13] promoted the cascade cyclization and formed the tetracycle **1** (Entries 6–7). *trans*-Fused decalin *trans*-**1**, as occurring in the sponge secondary metabolite cyclosmenospongine (Fig. 1),[14] was formed predominantly. We further evaluated Brønsted acids instead of the metal catalysts. Trifluoroacetic acid was not reactive (Entry 8), but triflic acid caused rapid decomposition of the starting material to polymeric products (Entry 9). Switching to nitromethane as solvent, allowed for the isolation of *trans*-**1** in modest yields (Entry 10).

In summary, we showed a concise enantioselective assembly of benzo[*d*]xanthenes illustrating in particular ruthenium-promoted cyclizations. Further efforts to address the formation of the corresponding *cis*-decalin system and applications to the synthesis of anti-influenza active natural product analogs are ongoing.

Acknowledgements

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Notes and references

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