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A novel one-step method for the reductive allylation of esters and the first total synthesis of (±)-erythrococcamide B

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ABSTRACT

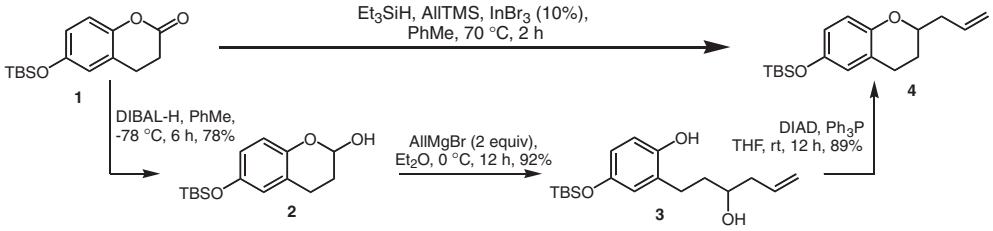
A novel and convenient one-step method for the reductive allylation of aliphatic and alicyclic esters using $InBr_3$ as a catalyst is reported. This methodology has also been applied in the first total synthesis of (±)-erythrococcamide B.

Indium(III) halides have recently been the subject of numerous studies leading to the development of novel methods. While the applications of dihaloindium hydrides have been reviewed,[1] newer methods have emerged, such as the preparation of alkynyl and allyl ketones from acyl chlorides,[2] propargyl alcohols and amines from aldehydes and *N*,*O*- or *N*,*S*-acetals,[3] synthesis of indoles and quinolines from 2-ethynylanilines,[4] cross-coupling of alcohols[5] or trimethylsilyl ethers[6] with allylsilanes, hydroarylation of arenes with styrenes,[7] reductive amination of carbonyl compounds[8] and one-step reduction of esters to ethers[9] and amides to amines.[10]

We were interested in the synthesis of 6-oxygenated 2-allyl chromans as precursors to novel heparin mimics.[11,12] While reaction of lactone **1** (Scheme 1) with allyl magnesium bromide gave only a mixture of starting material and a bis-allylated tertiary alcohol, reduction of **1** to lactol **2** using DIBAL-H, followed by allyl Grignard addition to form the secondary alcohol **3** and Mitsunobu cyclisation was successful. We wished to investigate shorter routes to this type of structure. In the one-step reduction of esters to ethers[9] with $InBr_3/Et_3SiH$ it was felt that the reduction may proceed via an oxonium intermediate and that this could be intercepted by allyltrimethylsilane. Herein we report a one-step method for the reductive allylation of a range of esters.

Initially, reduction of 3,4-dihydrocoumarin (**5**) to the unsubstituted chroman **7** was attempted using Sakai's conditions (Table 1, entries 1–3). Reduction only occurred successfully when the reaction mixture containing triethylsilane and **5** in toluene was heated to 70 °C, before addition of $InBr_3$ (0.1 equiv). Toluene was found to be superior to chloroform for the overall yield of the transformation and was preferred since it has a higher boiling point and addition of the catalyst led to a quite exothermic reaction.

Having established conditions for the reduction, reductive allylation was attempted using an excess of allyltrimethylsilane. We



Scheme 1.

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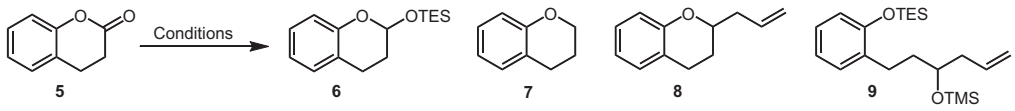
Table 1
Optimisation of the conditions for the reductive allylation



5 6 7 8 9

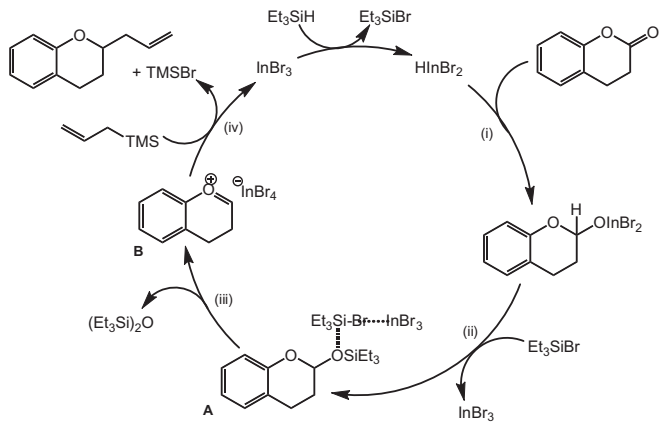
Entry	Additives (equiv)			Solvent	Ratio[a]					Yield[b](%)
	$InBr_3$	Triethylsilane	AllTMS		**5**	**6**	**7**	**8**	**9**	
1	0.05	4	—	$CHCl_3$	1	4	2	—	—	nd
2	0.1	4	—	$CHCl_3$	—	1	2.3	—	—	63
3	0.1	4	—	PhMe	—	—	1	—	—	93
4	0.1	1.5	2.5	PhMe	—	4	1	14	—	nd
5	0.1	1.1	2.5	$CHCl_3$	—	—	—	2	1	66
6	0.1	1.1	2.5	PhMe	—	—	—	1	—	79
7	0.1	1.1	2	PhMe	—	—	—	1	—	83[c]
8	0.1	1.1	1	PhMe	—	2.8	1	4.3	—	nd
9	—	1	2	PhMe	1	—	—	—	—	nd
10	0.1	—	2	PhMe	1	—	—	—	—	nd
11	0.1	1	—	PhMe	6.8	4	1	—		nd

[a] Ratios determined by ^1H NMR spectroscopy of the crude mixture.
[b] Isolated yields, nd = not determined.
[c] Reaction on a 50 mmol scale.

were pleased to observe the presence of the desired product **8** along with silylated lactol **6** and chroman **7** (entry 4). When the amount of triethylsilane introduced was decreased from 1.5 to 1.1 equiv (entries 5 and 6), the reductive allylation product was obtained exclusively. Toluene appeared again to be superior to chloroform (entries 5 and 6). A slight decrease in the excess of allyltrimethylsilane to 2 equiv did not decrease the yield (entry 7), however, with only 1 equiv, the proportion of hydroallylated product decreased dramatically (entry 8).

For mechanistic considerations, the reaction was conducted with either $InBr_3$, triethylsilane or allyltrimethylsilane left out of the mixture. While no reaction occurred in the absence of $InBr_3$ or triethylsilane (entries 9 and 10), reduction products were observed when no allyltrimethylsilane was added (entry 11). In addition, hexaethyldisiloxane could be isolated quantitatively from all reactions.

We, therefore, suggest that the reaction proceeds via (i) hydroindation of the ester by dibromoindium hydride (Scheme 2), followed by (ii) replacement of the dibromoindyl by a triethylsilyl group with regeneration of indium bromide. A complex of triethylsilyl bromide and indium bromide then allows (iii) elimination of the triethylsiloxyl from **A** to form the oxonium species **B**, which is then (iv) allylated by allyltrimethylsilane. In lower-yielding reactions (e.g., entry 5), the bis O-silylated by-product **9** was obtained. Presumably this arises from opening of the ring by elimination of phenoxide from intermediate **A**, with subsequent allylation of the aldehyde.



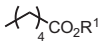
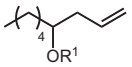
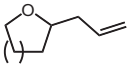
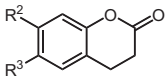
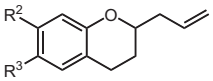
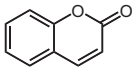
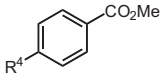
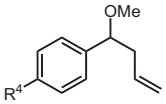
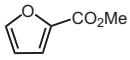
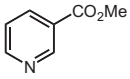
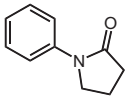
Scheme 2. Proposed mechanism for the reductive allylation of esters.

The reductive allylation methodology[13] was then extended to a representative range of esters (Table 2). Aliphatic and alicyclic esters (entries 1, 3–5) reacted smoothly to form the desired homoallylic ethers. Valeric acid (entry 2) showed no reaction at all even after 24 h. Derivatives of dihydrocoumarin also reacted well: the presence of a phenol (entry 8) seemed to slow down the reaction; this was attributed to the low solubility of the substrate. The *tert*-butylsilyl and methylenedioxy groups (entries 7 and 9) were stable under the reaction conditions. Introduction of $InBr_3$ when the mixture was already at 70 °C was found necessary to avoid cleavage of Lewis acid sensitive functionalities. For example, when $InBr_3$ was added before heating for the reductive allylation of methylenedioxychromanone **14b**, cleavage of the methylenedioxy group was observed. When coumarin (entry 10) was subjected to the conditions, conjugate reduction[1] was observed exclusively, presumably through a silyl ketene acetal, cleaved upon work-up, to form compound **5**, quantitatively. Reduction of aromatic esters with $InBr_3$/Et_3SiH is known to be slow and low-yielding and reductive allylation of aromatic (entries 11–13) and heteroaromatic esters (entries 14 and 15) gave poor results. Apart from methyl anisate (entry 12) which was hydroallylated in a rather low yield, other aromatic and heteroaromatic esters were inert to the conditions. Despite reports[10] suggesting that reduction of amides is possible using $InBr_3$/Et_3SiH, an attempt to apply the methodology to amide **21** (entry 16) was unsuccessful.

We then applied the new methodology in total synthesis. The isobutyl amides (+)-**22** and (+)-**23**, respectively, erythrococcamides A and B (Fig. 1), have been extracted from *Dinosperma erythrococca* and exhibited insecticidal activity.[14] The absolute configuration of the stereocentres is not known.

The synthesis (Scheme 3) started with sesamol (**24**), which was converted into the methylenedioxychromanone **14b** in 67% yield using methyl acrylate in TFA. Reductive allylation proceeded smoothly in a very good yield, followed by oxidative cleavage of the olefin using Lemieux–Von Rudloff's reagent[15] in a 77% yield. DCC/HOBt coupling with isobutylamine gave racemic **23** in 84% yield, 35% overall for four steps. The properties of our material were identical in all respects to those reported for the natural

Table 2
Reductive allylation of various substrates

Entry	Ester	Solvent, time	Product[a]	Yield[b](%)
1	 **10a**: R^1 = Me	PhMe, 2 h	 **11a**: R^1 = Me	99
2	**10b**: R^1 = H	PhMe, 24 h	**11b**: R^1 = H	NR
3	 **12a**: n = 1	PhMe-d_8, 2 h	 **13a**: n = 1	99
4	**12b**: n = 2	PhMe, 2 h	**13b**: n = 2	99
5	**12c**: n = 3	PhMe, 2 h	**13c**: n = 3	88
6	 **5**: R^2 = R^3 = H	PhMe, 2 h	 **8**: R^2 = R^3 = H	94 (83)[c]
7	**1**: R^2 = H, R^3 = OTBS	PhMe, 2 h	**4**: R^2 = H, R^3 = OTBS	92 (80)[c]
8	**14a**: R^2 = H, R^3 = OH	PhMe, 24 h	**15a**: R^2 = H, R^3 = OH	89
9	**14b**: R^2, R^3 = OCH_2O	PhMe, 2 h	**15b**: R^2, R^3 = OCH_2O	89 (81)[c]
10	 **16**	PhMe, 24 h	**5**	99
11	 **17a**: R^4 = H	PhMe, 24 h	 **18a**: R^4 = H	NR
12	**17b**: R^4 = 4-MeO	PhMe, 24 h	**18b**: R^4 = 4-MeO	25
13	**17c**: R^4 = 4-NO_2	PhMe, 24 h	**18c**: R^4 = 4-NO_2	NR
14	 **19**	PhMe, 24 h		NR
15	 **20**	PhMe, 24 h		NR
16	 **21**	PhMe, 72 h		NR

[a] All compounds were compared to literature precedents and all new compounds gave satisfactory spectral data.
[b] Conversions determined by ^{1}H NMR spectroscopy of the crude mixture, NR = no reaction.
[c] Isolated yields on a multigram scale reaction.

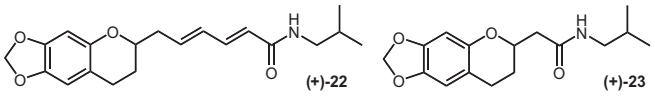
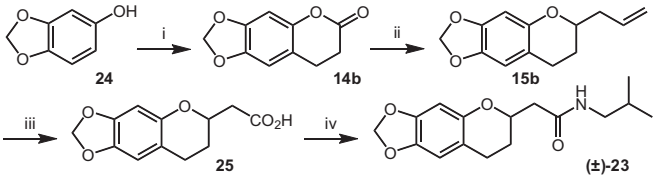


Figure 1. Structures of erythrococcamides A (**22**) and B (**23**).



Scheme 3. Total synthesis of erythrococcamide B. Reagents and conditions: (i) methyl acrylate (3 equiv), TFA, 70 °C, 6 h, 67%; (ii) $InBr_3$ (0.1 equiv), Et_3SiH (1.1 equiv), allyl-TMS (2.0 equiv), PhMe, 70 °C, 2 h, 81%; (iii) $KMnO_4$ (0.2 equiv), $NaIO_4$ (6.0 equiv), K_2CO_3 (1.5 equiv), ^{t}BuOH/water 1:1, rt, 3 h, 77%; (iv) DCC (1.1 equiv), HOBt (1.1 equiv), isobutylamine (1.5 equiv), CH_2Cl_2, 0 °C to rt, 12 h, 84%.

product, except for optical rotation.[14] This represents the first total synthesis of this natural product, which also confirms the proposed structure.

We have reported an efficient method for the one-step reductive allylation of esters, allowing rapid access to aliphatic and alicyclic homoallylic ethers. Studies are underway for the development of an enantioselective version of this reaction using Leighton's reagent.[16] We are also investigating the use of silyl ketene acetals and propargyl, allenyl and alkynyl silanes as nucleophiles.

Acknowledgements

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13. General procedure for the reductive allylation of esters: a solution of the ester (1 mmol, 1 equiv), triethylsilane (1.1 equiv) and allyltrimethylsilane (2 equiv) in toluene (3 mL) was heated to 70 °C and $InBr_3$ (0.1 equiv) was added in one portion. The mixture was left to stir at this temperature for 2 h and then poured into EtOAc (20 mL) containing water (0.1 mL). The solution was dried over $MgSO_4$, filtered through a pad of silica gel and concentrated, leading to a mixture of hexaethydisiloxane and the homoallylic ether, which could be purified by flash column chromatography, first using petroleum ether to elute the hexaethydisiloxane by-product and then a mixture EtOAc and petroleum ether, typically 1:6.
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