Catalytic Asymmetric Crotylation of Aldehydes: Application in Total Synthesis of (–)-Elisabethadione

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Abstract: A new, highly efficient Lewis base catalyst for a practical enantio- and diastereoselective crotylation of unsaturated aldehydes with *E*- and *Z*-crotyltrichlorosilanes has been developed. The method was employed as a key step in a novel asymmetric synthesis of bioactive serrulatane diterpene (–)-elisabethadione. Other strategic reactions for setting up the stereogenic centers included anionic oxy-Cope rearrangement and cationic cyclization. The synthetic route relies on simple, high yielding reactions and avoids use of protecting groups or chiral auxiliaries.

Secondary metabolites isolated from marine soft coral *Pseudopterogorgia elisabethae* exhibit a wide range of useful biological properties, which include anti-tubercular, anti-inflammatory, antimicrobial and cytotoxic activities,[1] while partially purified gorgonian extracts are used in commercial skin care products.[2] Selected representatives (**1**-**4**) of this family of marine natural products are shown in Figure 1.

Potent biological activity and the relatively simple structures of serrulatane diterpenes **1**, **2** and other analogues, augmented by the low abundance and scarcity of supply of these compounds from their natural sources, make them attractive synthetic targets for exploring their therapeutic potential.[3-6] However, the lack of functional groups near the stereogenic centres represents a significant challenge for stereoselective synthesis.

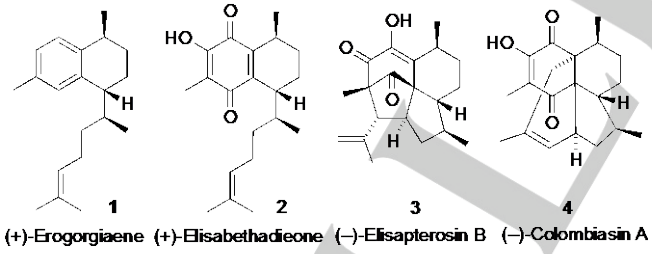

Figure 1. Selected *Pseudopterogorgia elisabethae* secondary metabolites.

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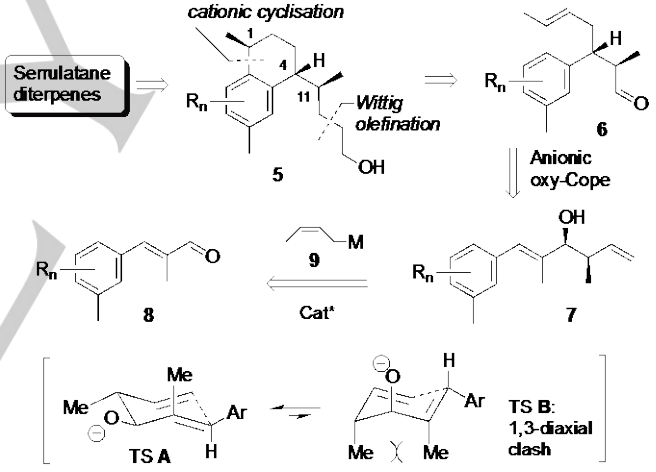
Our novel, general strategy for setting up the stereogenic centers at C-1, C-4 and C-11 of the serrulatane skeleton relies on enantioselective crotylation of aldehyde **8** to give *syn*-alcohol **7** followed by stereoselective anionic oxy-Cope rearrangement (AOC)[7] and ensuing cationic cyclization[8] (Scheme 1). Importantly, the α-methyl of the cinnamyl fragment and the *syn* configuration of the homoallylic alcohol **7** play a crucial role in assuring an efficient transfer of chirality during the AOC rearrangement. Of the two possible chair-like transition structures **A** and **B**, the TS **B** is disfavored due to the 1,3-pseudoaxial clash. Additionally, the TS **A** results in *E* alkene **6**, which keys in a formal 6-*endo* cyclization to afford the desired 1,4-*trans* tetralin **5**, as shown by Casey and co-workers.[8c].



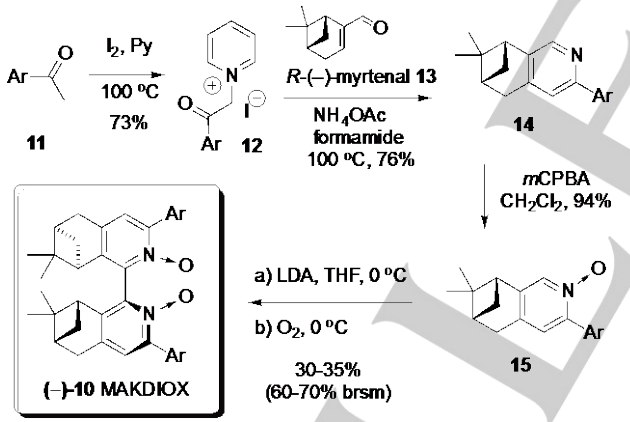
Scheme 1. Retrosynthetic analysis of serrulatane diterpenes.

The success of the strategy relies on the crotylation step (**8** → **7**, Scheme 1), by which chirality is introduced into the molecule. Herein, we present development of an efficient, practical and scalable method for catalytic asymmetric crotylation of unsaturated aldehydes, which is then successfully applied in the enantioselective total synthesis of serrulatane diterpene **2** from the respective α-methyl cinnamaldehyde **8** (Scheme 1).

Despite recent advances in the development of catalytic asymmetric allylation of carbonyl compounds with B- and Si-based allyl reagents,[9] including contribution from our group,[10] the related crotylation methodology remains a challenging problem and is still dominated by stoichiometric chiral B[11] and Si[12] reagents. The elegant catalytic method for crotylation of aldehydes or alcohols with butadiene reported by Krische[13] looks appealing but it does not match the enantio- and distereoselectivity level shown by the Type I boron and silicon reagents.[14] Brønsted acid catalyzed addition of commercial *E*-

and *Z*-crotylboronates to aldehydes represented a viable option,[15] however due to their relatively high cost and uninspiring preliminary attempts[16] our focus centered on a Lewis base catalyzed addition of easy to synthesize crotyltrichlorosilanes *Z*-**9a** and *E*-**9b** to unsaturated aldehydes.[17] It is well documented that chiral bipyridine-*N,N'*-dioxides are highly efficient catalysts for asymmetric allylation of aldehydes with allyltrichlorosilanes.[18] However, none of these catalysts are commercially available and their syntheses either involve lengthy sequences or give low overall yield, which makes them unsuitable for larger scale applications. Therefore, we now designed a new axially chiral bis-*N*-oxide **10** that can be synthesized in just 4 easy steps from inexpensive starting materials (Scheme 2).

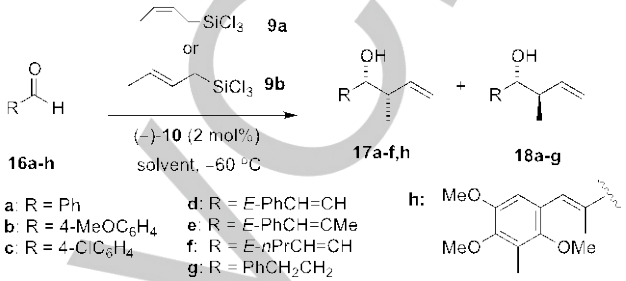
Synthesis of **10** commenced with preparation of the Kröhnke salt **12** by iodination of ketone **11** in pyridine (yield 73%).[10g] Kröhnke annulation of **12** with commercial (*R*)-myrtenal **13** in formamide in the presence of $AcONH_4$ produced isoquinoline **14** (yield 76%), which was converted to the respective *N*-oxide **15** by treatment with *m*CPBA (yield 94%). In the final step, an oxidative coupling[19] of **15** produced (–)-**10** as a single distereoisomer. Using 1 equiv. of LDA, **10** was commonly isolated in 30-35% yield together with ~50% of the unreacted **15**. Thus, based on the recovered starting material, the yield of **10** in this protocol is 60-70%. The absolute configuration of the catalyst has not been rigorously established but assumed to be as shown in Scheme 2 by comparison with literature data.[18h] For the new catalysts **10**, we propose the acronym MAKDIOX (includes initials of the co-author who developed its synthesis).



Scheme 2. Synthesis of (–)-**10** (Ar = 3,5-$(CF_3)_2$-C_6H_3).

The efficacy of the new catalyst **10** was assessed in the asymmetric crotylation of model aldehydes **16a-f** with crotyltrichlorosilanes *Z*-**9a** and *E*-**9b** (Table 1). Bis-*N*-oxide **10** turned out to be an extremely efficient catalyst producing excellent enantio- and diastereoselectivities over a whole range of aldehydes tested. Brief screening of solvents identified dichloromethane as the optimal choice; propionitrile came close second, while THF gave only modest enantioselectivities. Catalysts **10** proved particularly efficient with unsaturated aldehydes **16d-f** (entries 7-14), though with aliphatic **16g** enantioselectivity dropped (entry 15) representing a common trend in the catalytic allylation with allyltrichlorosilanes.[18] Diastereoselectivity generally reflected the geometrical purity of the starting crotyltrichlorosilanes *Z*-**9a** (*Z*/*E* 98:2) and *E*-**9b** (*E*/*Z* 95:5). However, in propionitrile cinnamyl aldehydes **16d** and **16e** appeared to react slightly faster with *Z*-**9a** giving the *syn*-enriched alcohols **17d** and **17e**, respectively (entries 8, 11).

Table 1. Catalytic asymmetric crotylation of aldehydes.[a]



Entry	**16**	**9a/9b**	Solvent	Yield (%)[d]	**17/18** (%)[b]	*ee* (%)[c]
1	**16a**	**9a**	DCM	94	98:2	92
2	**16a**	**9b**	DCM	91	4:96	96
3	**16b**	**9a**	DCM	86	98:2	92
4	**16b**	**9b**	DCM	81	4:96	96
5	**16c**	**9a**	DCM	93	95:5	85
6	**16c**	**9b**	DCM	89	5:95	91
7	**16d**	**9a**	DCM	83	98:2	95
8	**16d**	**9a**	EtCN	83	99:1	94
9	**16d**	**9b**	DCM	89	5:95	98
10	**16e**	**9a**	DCM	92	98:2	98
11	**16e**	**9a**	EtCN	92	99:1	97
12	**16e**	**9b**	DCM	88	3:97	99
13	**16f**	**9a**	DCM	80	98:2	98
14	**16f**	**9b**	DCM	82	4:96	96
15	**16g**	**9b**	DCM	55	4:96	50
16	**16h**	**9a**	EtCN	85	99:1	97
17[d]	**16h**	**9a**	EtCN	82	99:1	94

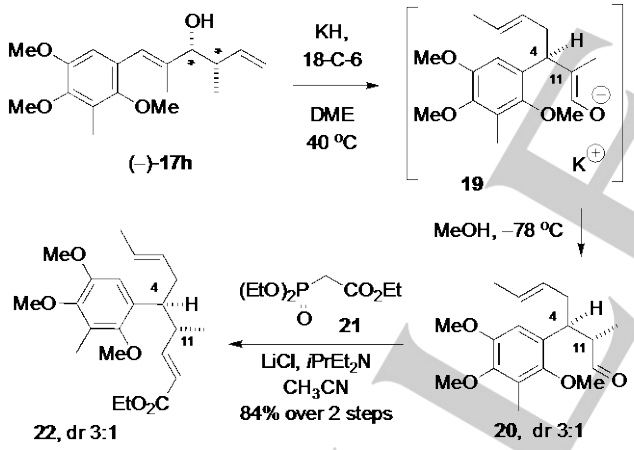
[a] Unless stated otherwise, the reactions were carried out on a 0.5 mmol scale at –60 °C for 24 h with 2 mol% loading of (–)-**10**, 1.7 eq of *Z*-**9a** (*Z*/*E* 98:2) or *E*-**9b** (*E*/*Z* 95:5) and 2.0 eq of *i*Pr_2EtN; [b] determined by 1H NMR or GC from the crude mixture; [c] ee of the major isomer, the absolute configuration is (1*R*,2*S*) for **17** and (1*R*,2*R*) for **18** (see Supporting Information); [d] the reaction was carried out on a 5 mmol scale, for 48 h.

Therefore, the asymmetric allylation of aldehyde **16h** required for the total synthesis of **2** with *Z*-**9a** was carried out in propionitrile. At 0.5 mmol scale the reaction afforded *syn*-

homoallylic alcohol **17h** in 85% yield and 97% ee (entry 16). Importantly, applying the same reaction conditions to a larger 5 mmol scale, excellent yield and enantioselectivity retained (yield 82%, ee 94%, entry 17) paving the way for the asymmetric synthesis of **2**.

To progress with the total synthesis, enantiopure alcohol (–)-**17h** was subjected to the AOC rearrangement using excess KH and 1 equiv. of 18-crown-6 in DME at 40 °C for 5 h (Scheme 3). Stereogenic center C-4 in **20** is created during the rearrangement, whereas C-11 is formed upon protonation of enolate **19**.[20] After a brief optimization of the quenching conditions, the best results were achieved by cooling the reaction mixture to −78 °C, followed by a quick addition of MeOH. In this way, **20** was obtained with dr 3:1. To minimize manipulation of the oxidation-prone aldehyde and to avoid epimerization at C-11, crude **20** was subjected to Horner–Wadsworth–Emmons alkenylation conditions[21] using phosphonate **21**. The corresponding α,β-unsaturated ester **22** was obtained in 84% yield over 2 steps (dr 3:1). The diastereoisomers were not separable at this stage and the synthesis was continued with the mixture.

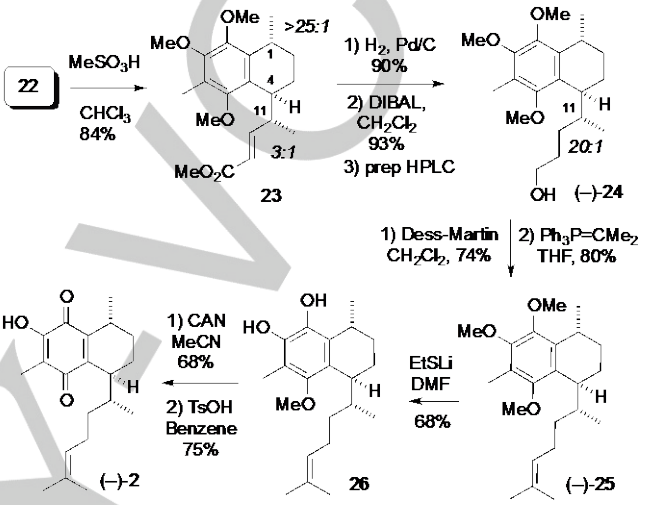
The final stereogenic centre C-1 was installed through the cationic cyclization of **22** upon treatment with $MeSO_3H$ to afford the tetralin derivative **23** (Scheme 4). Importantly, the reaction proceeded with high stereoselectivity giving only the trans isomer (dr > 25:1) in 84% yield, as evidenced by 1H NMR spectroscopy.



Scheme 3. Anionic oxy-Cope rearrangement of (–)-**17g**.

Next, hydrogenation of the double bond in **23** using H-Cube (10% Pd/C) followed by reduction of the ester with DIBAL-H afforded primary alcohol **24** as a 3:1 mixture of C-11 isomers in 84% overall yield. At this point, the isomers showed slightly different R_f values on TLC but gave a clear baseline separation on an analytical HPLC column. Therefore, separation of 500 mg of the mixture was successfully accomplished by preparative HPLC to furnish pure (–)-**24** (dr 20:1). Since this intermediate was employed by Davies and co-workers[4,5g] in their synthesis of compounds **2**-**4**, it marks the formal total syntheses of all these secondary metabolites.[22]

To complete the synthesis of (–)-**2**, alcohol (–)-**24** was oxidized to the respective aldehyde using Dess–Martin periodinane (DMP) followed by Wittig alkenylation to afford (–)-**25**. Next, as a possible shortcut to (–)-elisabethadione **2**, a one-pot sequence involving demethylation of (–)-**25** with BBr_3 followed by aerobic oxidation was examined.[8e] A clean demethylation did take place but it was accompanied by hydrobromination of the double bond. All attempts to eliminate HBr from this product led to extensive decomposition.



Scheme 4. Completion of the total synthesis of (-)-elisabethadione **2**.

Therefore, the synthesis continued along the route described by Davies.[4] Partial deprotection of (–)-**25** using EtSLi yielded the corresponding bisphenol **26** in 68% yield. Importantly, in the racemic variant of the synthesis, compound **26**, obtained as a 2:1 mixture of isomers, gave crystals suitable for X-ray crystallographic analysis,[23] which confirmed the assigned relative configuration of the major isomer (Figure 2) and also showed that the two isomers differ only by the configuration at C-11.

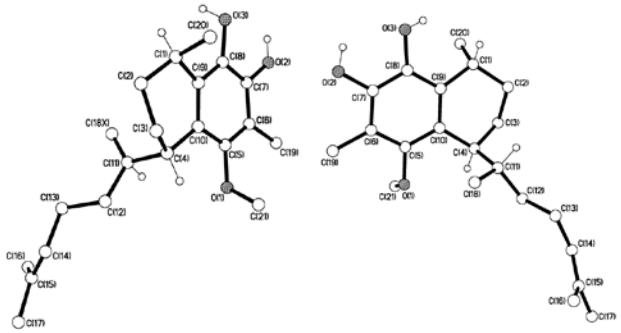


Figure 2. Crystal structure of **26** and *epi*-**26** highlighting relative stereochemistry. The isomers differ only by the position of C(18) and H(11) on C(11), manifested by disorder at C(11).

In the endgame, bisphenol **26** was first oxidized to the respective *ortho*-quinone by CAN, followed by treatment with TsOH in benzene to afford (–)-elisabethadione **2** (dr 20:1, 20% yield from alcohol (–)-**24**), the enantiomer of the natural product. The synthesized compound exhibited $[\alpha]_D$ = –267 (c 0.16, $CHCl_3$), opposite in sign but closely matching the absolute value reported by Davies: $[\alpha]_D$ = +278 (c 0.58, $CHCl_3$).[4] Other spectral data were also identical to those reported in literature.[4]

In conclusion, we developed a new bis-*N*-oxide catalyst for a scalable, highly enantioselective crotylation of unsaturated aldehydes with *E*- and *Z*-crotyltrichlorosilanes. Salient features of the new catalyst are: (i) the synthesis involves four easy steps from inexpensive, commercially available starting materials and is amendable to scale up; (ii) the new protocol is highly stereoselective and does not require chiral resolution or separation of diastereoisomers. The enantioselective crotylation method plays a pivotal role in a novel strategy for assembling the structural core of serrulatane diterpenes, which was illustrated by the asymmetric total synthesis of *ent*-elisabethadione **2**, a member of the *Pseudopterogorgia elisabethae* family of bioactive marine natural products. Other key steps to install the challenging stereogenic centers include anionic oxy-Cope rearrangement and cationic cyclization. The synthetic route relies on simple, high yielding reactions and avoids use of protecting groups or chiral auxiliaries. A more detailed investigation into the scope of the catalytic asymmetric crotylation and development of new synthetic applications are currently underway.

Acknowledgements

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Keywords: allylation · asymmetric catalysis· rearrangement · stereoselectivity · total synthesis

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[16] At 0.5 mmol scale, crotylation of **16g** with *Z*-crotylboronic acid pinacol ester using chiral phosphoric acid (*R*)-TRIP (10 mol%), refs [14d, 14e], produced alcohol **17g** in 78% yield and 90% ee. However, at a larger 5 mmol scale, under the same conditions, the reaction turned sluggish and was accompanied by a substantial drop in enantioselectivity (40% ee).

[17] Isomerically enriched **9a** and **9b** are routinely synthesized in our laboratory on a 10 g scale by adapting the following protocols: a) J. Tsuji, M. Hara, K. Ohno, *Tetrahedron* **1974**, *30*, 2143-2146; b) M. Kira, T. Hino, H. Sakurai, *Tetrahedron Lett*. **1989**, *30*, 1099-1102; c) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 3513-3526. For details, see Supporting Information.

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[20] In model studies using homoallylic alcohol derived from simple α-methyl cinnamaldehyde, variation of quenching conditions resulted in diastereomeric ratios between 3:1 and 1:2.

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[22] Overall, alcohol (–)-**24** was synthesized in 10 steps from 1,3,4-trimethoxybenzene. Davies and co-workers (refs 4,5g) obtained (+)-**24** from the same starting material in the same number of steps but through a different set of reactions.

[23] Crystal Data for **26**: $C_{21}H_{32}O_3$, *Mr* = 332.46, 0.86 × 0.60 × 0.04 mm^3, monoclinic, $P2_1/c$, *a* = 18.179(3), *b* = 7.3992(10), *c* = 14.334(2) Å, *β* = 99.856(2)°, *V* = 1899.6(5) $Å^3$, *Z* = 4, ρ_{calcd} = 1.162 Mg m^{-3}, *μ*(Mo-Kα) = 0.08 mm^{-1}, λ = 0.71073 Å, *T* = 150K, $2\theta_{max}$ = 61.2° , 21151 data measured, 5734 independent reflections, R_{int} = 0.035 , *R* [$F^2 > 2\sigma(F^2)$], 4047 data] = 0.049, *wR* [F^2, all data] = 0.143, residual electron density within ± 0.52 e $Å^{-3}$. For details, see Supporting Information.

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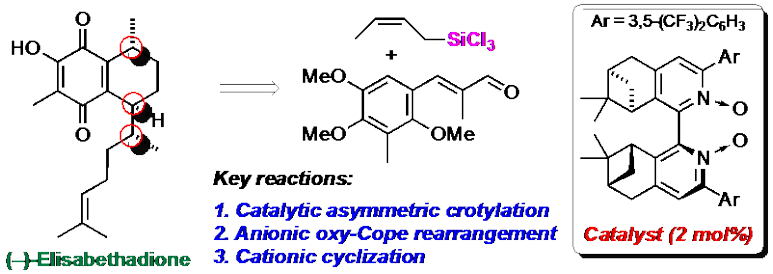

A new catalyst for a practical and scalable enantio- and diastereoselective crotylation of unsaturated aldehydes has been developed. The method was employed as a key step in a novel asymmetric route to bioactive serrulatane diterpene (–)-elisabethadione. Other strategic reactions for setting up the stereogenic centers included anionic oxy-Cope rearrangement and cationic cyclization.

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