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TiF_4-mediated biomimetic alkylation–cyclization cascade reaction of 2-trimethylsilylmethyl-1,5-dienes with aldehydes

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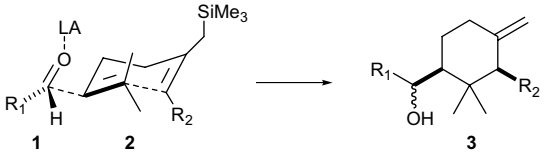
Abstract—TiF_4 has proven to be the Lewis acid of choice for promoting the biomimetic addition of 2-trimethylsilylmethyl-1,5-dienes to aliphatic aldehydes with concomitant cyclization. 1,3-*cis*-Disubstituted methylenecyclohexanes are thus produced in good yields and high diastereoselectivity. The reaction appears to proceed via a highly concerted mechanism involving a chair-like transition state.

In the suggested biosynthesis of several terpenoids, such as saponaceolides[1] and mispyric acid,[2] core structures are assembled by cyclization of a 1,5-diene moiety promoted by the electrophilic addition of a formal terpenoid carbocation species. The coupling has been proposed to occur through a highly ordered arrangement leading to a *cis*-1,3-alkylated six-membered ring. Early sporadic attempts to reproduce this elegant biochemical process in vitro, though imaginative, were, however of limited synthetic applicability. In fact, a mixture of cyclized and non-cyclized products were usually attained,[3] with unsatisfactory regio- and diastereoselectivity.

Along this line, in a preliminary study, we first reported the cyclization of a 1,5-diene (**2**, $R_2 = CH_2OAc$) promoted by electrophilic addition of $TiCl_4$-complexed aliphatic aldehydes (Scheme 1).[4]



Scheme 1.

The latter results were still rather a proof of concept than a real tool for the synthetic community, due to the cyclization modest yields (⩽35% based on the starting aldehyde) and variable amounts of contaminating protodesilylated and chlorinated adducts. Therefore, with the goal to develop a new useful approach to the total synthesis of natural products, we decided to further screen several combinations of the three reaction components, namely, a Lewis acid, diene **2**, and aldehyde **1**, with respect to which yields were optimized. The results obtained with different aromatic and aliphatic aldehydes, Lewis acids (LA = Me_2AlCl, Me_2AlCl–$TiCl_4$, Me_3SiOTf, TiF_4, $SnCl_4$, $Sc(OTf)_3$, and $Yb(OTf_3)$) and substituted dienes ($R_2 = CH_2OAc$, CH_2OH, and COOR) indicated that the course of the reaction, though rather unpredictably, varied with the electron density of the allylsilane moiety, imparted by the R_2 substituent, and the hardness of the complexed aldehyde, mainly determined by the Lewis acid used (Scheme 1). Extensive experimentation was thus needed to finely tune the electronic characteristic of the reactants to drive the cyclization to a useful preparative method. At last we discovered that TiF_4[5] efficiently promotes the addition–cyclization of 1-alkoxycarbonyl-2-trimethylsilylmethyl-1,5-dienes **2** ($R_2 = CO_2R'$) to aliphatic aldehydes (**1**), affording 1,3-disubstituted methylenecyclohexane derivatives (**3**) in good yields and high cis-diastereoselectivity (Scheme 1 and Table 1). The optimal molar ratio of **1**, **2**, and TiF_4 was eventually adjusted to 1:2:4, respectively, with initial exposure of the aldehyde to TiF_4 at −40 °C for 10 min prior to diene **2** ($R_2 = CO_2Me$)[6,7] addition at 0 °C.[8] Addition of diene

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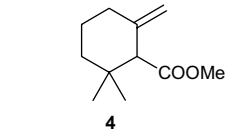
Table 1. Results of the reactions of diene **2** ($R_2 = CO_2Me$) with aldehydes

Entry	Aldehyde	Yield[a]	*cis*/*trans* Ratio[b]	Carbinol diastereomeric ratio[b]	
				cis **5a**+**6a**:**6b**	*trans*[c] **7**
1	$PhCH_2CH_2CHO$ (**8**)	50	87:13	69:31	66:34
2	Cy-CH_2CHO	64	87:13	73:27	61:39
3	Me_2CHCH_2CHO	82	85:15	75:25	70:30
4	*n*-Hexyl-CHO	85	94:6	80:20	ND
5	Cy-CHO	42	ND	ND	ND
6	Me_3C–CH_2CHO	40	ND	ND	ND

[a] Combined isolated yields of products **5**+**6**+**7** with respect to the aldehyde.
[b] **5**+**6**:**7**, determined by GC for entries 1 and 2, and by NMR and isolated yields for entries 3 and 4.
[c] The stereochemistry at C′1 of carbinols **7a**,**b** was not established.

2 to aldehydes **1** competed with its concurrent proton-initiated cyclization to *exo*-methylenecyclohexane **4**. In fact, the addition was minimal at −40 °C, while it occurred readily at 0 °C with an excess diene.



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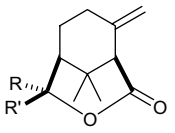
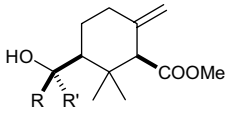
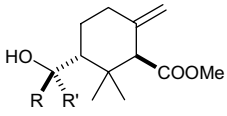


5a R=H, R'=alkyl
5b R=alkyl, R'=H
5c R=H, R'=isobutyl
5d R=isobutyl, R'=H



6a R=H, R'=alkyl
6b R'=H, R=alkyl



7a R=H, R'=alkyl
7b R'=H, R=alkyl

On the other hand, TiF_4-induced self-condensation of aldehyde **1** was negligible when the complex with the Lewis acid was formed at −40 °C.

MeCN was the solvent of choice given the insolubility of TiF_4 in other aprotic solvents. This medium had the additional advantage to tune the Lewis acid strength so finely that polymerization of TiF_4-complexed aldehyde was unimportant at −40 °C. By contrast, in a non-coordinating solvent, like DCM, aldehyde polymerization occurred readily, even at −78 °C.

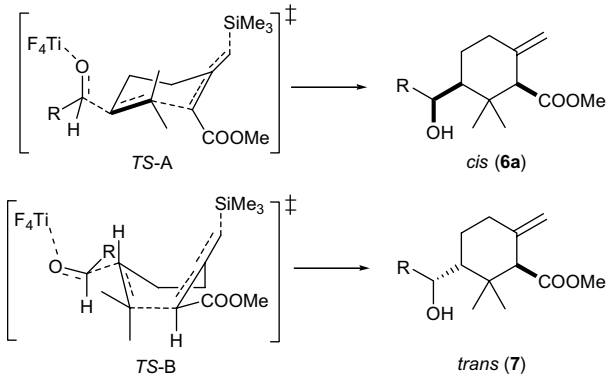
The superior reactivity of TiF_4 with respect to other Lewis acid catalysts has been attributed to the high electronegativity of fluorine.[5] Moreover, the high strength of the Ti–F bond[5] was an additional bonus to avoid the formation of halogenated side-products, which, instead, contaminated analogous $TiCl_4$ or $SnCl_4$-promoted cyclization products.[3,4]

Both the cis- and the trans-products comprised the two epimers at the newly formed carbinol stereocenter, namely alcohols **6a**,**b** and **7a**,**b**, respectively. Compound **6a**, the more abundant of the two epimeric alcohols in the cis-pair, slowly gave lactone **5a** under reaction conditions, whereas carbinol **6b** lactonized to **5b** only upon exposure to a catalytic amount of *p*-TsOH in CH_2Cl_2 overnight. Indeed, for preparative purposes, the crude reaction mixture was treated with *p*-TsOH, so that lactones **5a**,**b** were easily separated from unreacted *trans*-hydroxyesters **7a**,**b** by column chromatography.[8]

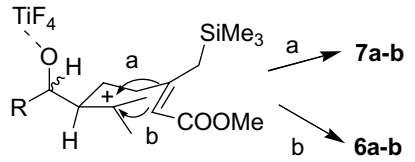
Structure assignments to the cis (**6a**,**b**) and the trans (**7a**,**b**) stereoisomers were based on the highly diagnostic ^1H NMR signals of the *exo* olefin protons,[9] while NOESY experiments on lactones **5a** and **b**, respectively, indicated the structure of each *cis*-hydroxyester, **6a** and **b**, respectively.

The ratio of diastereomers **6**+**5** to **7** did not change significantly on prolonged exposure to TiF_4 or *p*-TsOH, according to a kinetic control of the reaction diastereoselectivity.

The results obtained from cyclization of the model aldehydes suggest that major *cis*-compounds **6a**,**b** likely arise from a highly concerted mechanism involving a chair-like transition state (TS-A in Scheme 2). A synclinal arrangement of aldehyde and olefin double bonds, with an *anti* orientation of the approaching aldehyde R group with respect to the bulky geminal dimethyl group, would thus explain the preferential stereochemistry at C-1′ of the cis-compounds, namely that of **6a**.[10,11] Conversely, a higher energy boat-like TS (TS-B in Scheme 2) may account for the formation of the minor trans-stereoisomers **7a**,**b**.

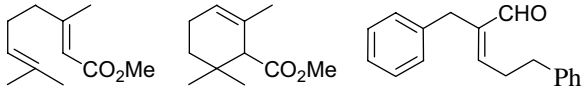


Scheme 2.



Scheme 3.

An alternative non-concerted mechanism (Scheme 3), involving a fully developed tertiary carbenium ion species arising from addition of the distant double bond of **2** to the TiF_4-complexed aldehyde, prior to cyclization, was ruled out on the basis of the results obtained by substituting diene **2** ($R_2 = CO_2Me$) with methyl geraniate **9** under standard conditions.[8] In fact, the reaction with 3-phenylpropanal **8** afforded, as the main products, methyl cyclogeraniate **10** (50% from **9**), arising from proton-initiated cyclization of the diene, and unsaturated aldehyde **11** (42% from **8**), due to the aldol self-condensation of the aldehyde.



9 **10** **11**

By contrast, under these conditions, the expected products of the alkylation–cyclization reaction, namely, lactone **5a** ($R' = PhCH_2CH_2$) and hydroxy esters **6** and **7** R or ($R' = PhCH_2CH_2$), were produced in only 4% and 2% yields, respectively (carbinol stereochemistry undetermined).

It thus appears evident that the allylsilyl group of diene **2** ($R_2 = CO_2Me$), in addition to being an effective terminating unit and controlling the cyclization regioselectivity,[4,6,12] possibly increases the electron density of the distant olefin, via through space interaction of the double bonds.[13]

In conclusion, in this letter we have described the first example of an efficient and stereoselective biomimetic 1,5-diene cyclization promoted by an external electrophilic carbenium species, namely, a Lewis acid complexed aliphatic aldehyde. In comparison with other Lewis acids, the use of TiF_4 appears to be crucial for attaining good yields with respect to the starting aldehyde and high cis-diastereoselectivity of the products. This new methodology can become a useful tool for the synthesis of different natural products. Our own applications in total synthesis will be reported in due time.

Acknowledgements

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7. Similar results were obtained with other simple esters ($R_2 = Et$ or Pr).
8. The reaction with isovaleraldehyde (**1**, $R_1 =$ isobutyl) describes the general preparative procedure. A solution of isovaleraldehyde (**1**, $R_1 =$ isobutyl) (67.2 mg, 0.786 mmol) in dry CH_3CN (8 mL) containing 4 Å MS (about 40 mg), under an Ar atmosphere, was cooled to −40 °C and TiF_4 390 mg, (3.14 mmol) was added in one portion. After 10 min, a solution of 1,5-diene **2** ($R_2 = CO_2Me$)[6] in MeCN (400 mg in 1 mL, 1.57 mmol) was added and the temperature was raised to 0 °C. The reaction was stirred for 4 h at the same temperature, then quenched with 20 mL of a 1:1 mixture of 5% aqueous $NaHCO_3$ and brine, and diluted with diethyl ether (20 mL). The aqueous phase was extracted with diethyl ether (3×30 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude residue (412 mg), dissolved in CH_2Cl_2 (70 mL), was exposed to *p*-TsOH (13 mg) under stirring at rt overnight. The reaction mixture was washed with satd aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. The salt was filtered off and the filtrate was concentrated in vacuo. The resulting residue was separated by flash chromatography on silica gel. Elution with a hexane–EtOAc gradient (from 99:1 to 90:10) afforded, in the order, lactone **5c** (87 mg, 47% with respect to isovaleraldehyde) and **5d** (28 mg, 15% with respect to isovaleraldehyde), each uncontaminated by the epimeric *trans*-hydroxyesters **7** ($R_1 =$ isobutyl). Lactone **5c**: IR (neat) ν (tilde) 2955, 2970, 1740, 1748, 1650, 1467, 1368, 1254, 1224, 1069, 1029, 920, 897 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 0.96 (d, $J = 6.5$ Hz, 3H), 0.97 (d, $J = 6.5$ Hz, 3H), 1.04 (s, 3H), 1.18 (s, 3H), 1.3–1.45 (m, 2H), 1.7–1.95 (m, 4H), 2.15–2.28 (m, 2H), 2.95 (br s, 1H), 4.75 (m, 1H), 4.91 (br s, 2H); ^{13}C NMR (75 MHz $CDCl_3$, TMS) δ 172.1 (s), 142.2 (s), 112.2 (t), 79.0 (d), 59.3 (d), 41.5 (t), 39.6 (d),

34.9 (s), 27.9 (t), 26.9 (q), 25.1 (q), 24.2 (d), 22.9 (q), 22.1 (q), 21.3 (t); GC–MS *m/z* (relative intensity) 236 (M^+, 6.5), 193 (23.9), 177 (3.0), 149 (2.0), 135 (4.3), 121 (100), 107 (11.2), 93 (11.7), 79 (10.8), 67 (5.1), 55 (5.9). $C_{15}H_{24}O_2$ calcd: C, 76.23; H, 10.24. Found: C, 76.33; H, 10.12. Lactone **5d**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS), δ 0.96 (d, $J = 6.5$ Hz, 3H), 0.97 (d, $J = 6.5$ Hz, 3H), 0.98 (s, 3H), 1.14 (s, 3H), 1.4–1.56 (m, 2H), 1.75–2.1 (m, 4H), 2.18–2.36 (m, 2H), 2.91 (br s, 1H), 4.42 (m, 1H), 4.92 (br s, 2H); ^{13}C NMR (75 MHz $CDCl_3$, TMS) δ 171.8 (s), 141.5 (s), 113.6 (t), 84.0 (d), 58.5 (d), 46.7 (t), 40.3 (d), 33.8 (s), 29.1 (t), 28.4 (q), 27.1 (t), 25.5 (q), 24.8 (d), 22.8 (q), 21.9 (q). $C_{15}H_{24}O_2$ calcd: C, 76.23; H, 10.24. Found: C, 76.38; H, 10.32.

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