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Intramolecular $TiCl_4$-mediated cyclization reaction of β-hydroxy alkynyl acetals

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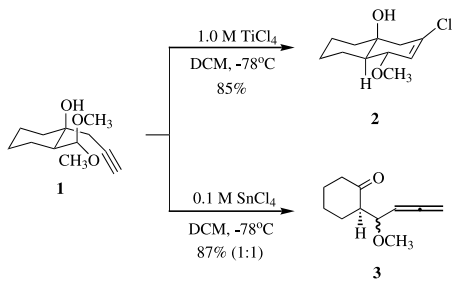
Abstract—Intramolecular $TiCl_4$-mediated cyclization reaction of 1,1-dimethoxy-3-hydroxy-hex-5-yne derivatives produced *anti*-1-hydroxy-3-methoxy-cyclohex-5-ene derivatives with high diastereoselectivity via antiperiplanar manner on pseudo six-membered chair like conformation (transition state A).

The preparation of both carbocycles and heterocycles using the Lewis acid-mediated cyclization reaction of acetals with the participation of alkynes as nucleophiles has been well documented,[1] notably through the extensive investigations of the Johnson group.[1,2] More recently, the Lewis acid-mediated cleavage[3] of acetals and chiral acetals has been the subject of numerous investigations and has become a useful tool for the asymmetric synthesis of secondary alcohols and the preparation of medium and large ring compounds.[4]

The mechanism of the Lewis acid-mediated nucleophilic substitution of acetals is a recent topic of interest. Denmark reported that sterically unhindered aliphatic acetals underwent intramolecular S_N2-type substitution with the aid of a mild Lewis acid.[3i] In contrast, Sammakia observed that dimethyl acetals underwent intermolecular allylation via an oxocarbenium ion using any kind of Lewis acid.[3g] To our knowledge, however, there has been one example[4b] reported on the intramolecular Lewis acid-mediated cyclization of alkynyl acetals. Overman et al. reported a ring-enlarging cyclopentane annulation that involves the reaction of an alkynyl acetal with $SnCl_4$. This is believed to proceed by a cationic cyclization–pinacol rearrangement sequence but its stereoselectivity is not satisfactory.

We speculated that when the hydroxy group is present at the β-position of the acetal, a Lewis acid-mediated cyclization reaction by alkyne could diastereoselectively proceed via antiperiplanar attack on oxocarbenium ion generated from chelation of β-hydroxy moiety and acetal with Lewis acid. Consequently, we decided to investigate the stereochemical course of the intramolecular Lewis acid-mediated cyclization reaction of β-hydroxy alkynyl acetals. In the initial study testing of our hypothesis, the combination of alkyne and $TiCl_4$ or $SnCl_4$ was chosen for investigation in conjunction with β-hydroxy acetal electrophiles. We are delighted to report herein on the reaction of $TiCl_4$ and β-hydroxy alkynyl acetal, which, in most cases, proceeds with excellent diastereoselectivity (Scheme 1).



Scheme 1.

The first, when readily available β-hydroxy alkynyl acetal **1** was treated with $TiCl_4$ at −78°C, *anti*-1,3-dihydroxycyclohexene compound **2** was obtained as a single diastereomer in 85% yield. The *anti*-orientation of the two hydroxy moieties of **2** was confirmed by a single-crystal X-ray diffraction study (Fig. 1). But, the treatment of **1** with $SnCl_4$ at −78°C afforded an allene

Keywords: 1,3-diaxial alcohol; β-hydroxy alkynyl acetal; intramolecular cyclization; Lewis acid; stereocontrol.

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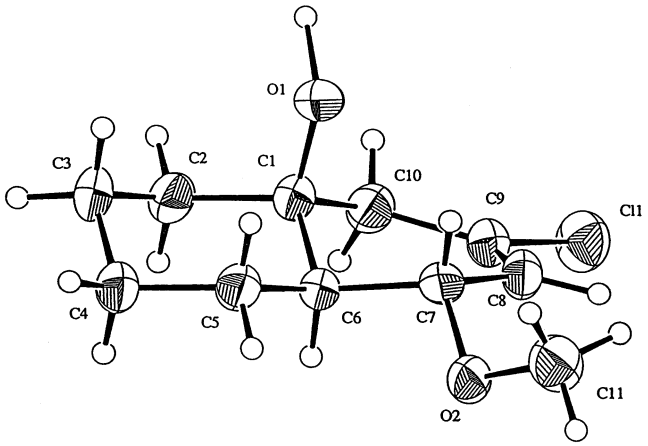


Fig. 1. X-Ray crystal structure of **2**.

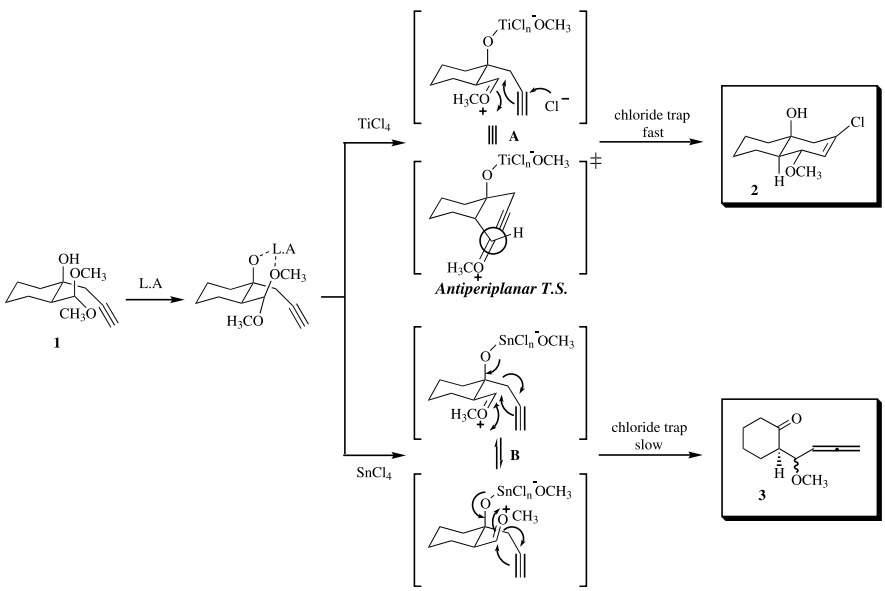
compound **3** as a diastereomeric mixture (1:1) in 87% yield.

The mechanistic basis for these results of the Lewis acid-mediated intramolecular nucleophilic cyclization is unclear; however, we propose the following mechanism shown in Scheme 2.

When β-hydroxy alkynyl acetal is treated with Lewis acid, oxocarbenium ion is generated from the chelation of β-hydroxy moiety and acetal with Lewis acid. As the alkyne attacks the oxocarbenium, a carbenium ion develops which has to be trapped by chloride in order to produce the desired cyclization product. If the trapping by chloride is slow, then push–pull fragmentation to the allene compound could be observed. This differentiation could be due to a difference in the availability of halogen, which in turn could depend on the Lewis acid, as such, both reactions could proceed via a common intermediate with the difference in product arising from a different course for the reaction after the C–C bond is formed. In the case of $TiCl_4$, the single diastereomer **2** may suggest highly diastereoselective cyclization via antiperiplanar manner on pseudo six-membered chair like conformation (transition state **A**). In contrast to $TiCl_4$, when the alkynyl acetal is reacted with $SnCl_4$, an allene compound **3** is produced as a diastereomeric mixture (1:1).[5] It demonstrates that the reaction proceeds via an oxocarbenium ion intermediate **B** by a slow chloride trap. In an effort to investigate the scope and limitation of this methodology, several 1,1-dimethoxy-3-hydroxy-hex-5-yne derivatives[6] were treated with $TiCl_4$ or $SnCl_4$. The results of this reaction are summarized in Table 1.

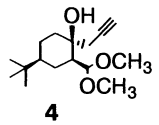
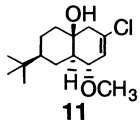
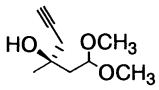
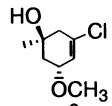
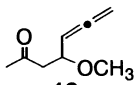
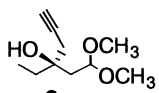
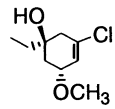
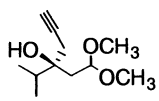
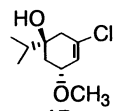
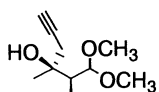
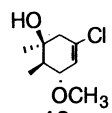
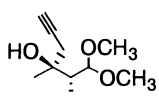
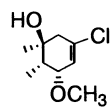
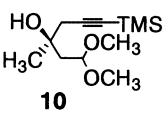
All reactions of entries **1**–**6** with $TiCl_4$ at −78°C afforded *anti*-1-hydroxy-3-methoxy-cyclohex-5-ene derivatives as a single diastereomer on ^1H NMR (500 MHz). To our knowledge, these present the first examples of intramolecular $TiCl_4$-mediated cyclization reaction that form *anti*-1,3-dihydroxy-cyclohexene products with high diastereoselectivity. However, not all substrates could be induced to undergo cyclization, even though the structures were quite similar. In the case of the alkynyl acetal containing the TMS group attached to the terminal alkyne carbon, it did not undergo cyclization (entry **7**) and this unreactivity might be due to the steric hindrance between TMS-alkyne and acetal group.

In conclusion, we provided the first example of highly diastereoselective intramolecular $TiCl_4$-mediated cyclization reaction of β-hydroxy alkynylacetal derivatives. The reaction can be realized by an appropriate condition of nucleophile (alkyne) and the Lewis acid ($TiCl_4$) and lend itself to the synthesis of a variety of substituted *anti*-1,3-dihydroxycyclohexane systems. Further studies and applications of this reaction will be reported in due course.



Scheme 2.

Table 1. Intramolecular Lewis acid-mediated cyclization of 1,1-dimethoxy-3-hydroxy-hex-5-yne derivates[7]

Entry	Substrate	Conditions[a]	Product	% Yield[b]
1	 **4**	A	 **11**	88
2	 **5**	A	 **12**[c]	74
		B	 **13**	68
3	 **6**	A	 **14**	75
4	 **7**	A	 **15**	72
5	 **8**	A	 **16**	70
6	 **9**	A	 **17**	67
7	 **10**	A	NR[d]	-

[a] A: 1.0 M $TiCl_4$ (1.1 equiv. in CH_2Cl_2, –78°C), B: 0.1 M $SnCl_4$ (1.1 equiv. in CH_2Cl_2, –78°C).
[b] Yield refer to isolated and chromatographically pure products.
[c] The stereochemistry was confirmed by NOE experiment.[8]
[d] No reaction.

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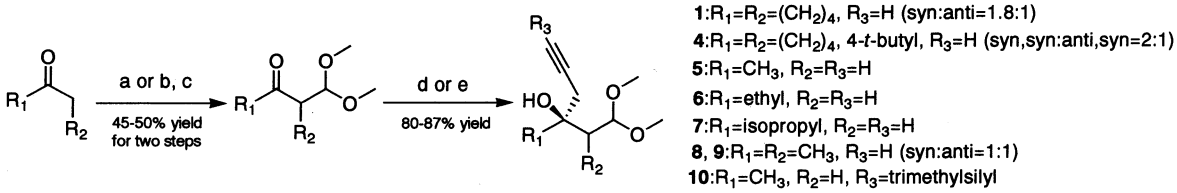
References

1. For reviews, see: (a) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043; (b) Overman, L. E.; Sharp, M, J. *J. Am. Chem. Soc.* **1988**, *110*, 612; (c) Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* **1989**, *37*, 57; (d) Funk, R. L.; Fitzgerald, J. F.; Olmstead, T. A.; Wos, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 8849. For oxacycles, see: (e) Melany, M. L.; Lock, G. A.; Thomspon, D. W. *J. Org. Chem.* **1985**, *50*, 3925; (f) Lolkema, L. D. M.; Hiemstra, H.; Semeyn, C.; Speckamp, W. N. *Tetrahedron*. **1994**, *50*, 7115.
2. For reviews, see: (a) Johnson, W. S.; Kinnel, R. B. *J. Am. Chem. Soc.* **1966**, *88*, 3861; (b) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51; (c) Johnson, W. S.; Ward, C. E.;

Boots, S. G.; Gravestock, M. B.; Markezich, R. L.; McCarry, B. E.; Okorie, D. A.; Parry, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 88, and other papers in this series.
3. (a) McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7371; (b) Sekizaki, H.; Jung, M.; McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7372; (c) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088; (d) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107; (e) Corcoran, R. C. *Tetrahedron Lett.* **1990**, *31*, 2101; (f) Molander, G. A.; Haar, J. P., Jr. *J. Am. Chem. Soc.* **1993**, *115*, 40; (g) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915. For recent review, see: (h) Alexakis, A.; Mangency, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477; (i) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089; (j) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998; (k) Kinugasa, M.; Harada, T.; Oku, A. *J. Am. Chem. Soc.* **1997**, *119*, 9067; (l) Harada, T.; Nakamura, T.; Kinugasa, M.; Oku, A. *J. Org. Chem.* **1999**, *64*, 7594, and reference cited therein.
4. (a) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 6556; (b) Johnson, T. O.; Overman, L. E. *Tetrahedron Lett.* **1991**, *32*, 7361; (c) Johnson, W. S.; Plummer, M. S.; Reddy, S. P.; Bartlett, W. R. *J. Am. Chem. Soc.* **1993**, *115*, 515; (d) Hirst, G. C.; Johnson, T. O.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992; (e) Trost, B. M.; Chen, D. W. C. *J. Am. Chem. Soc.* **1996**, *118*, 12541; (f) Ando, S.; Minor, K. P.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 6379; (g) Morihira, K.; Hara, R.; Kuwasara, S.; Nisimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 12980; (i) Hara, R.; Furukawa, T.; Kashima, H.; Kusama, H.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1999**, *121*, 3072.
5. For a similar discussion, see: Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. *J. Am. Chem. Soc.* **1998**, *120*, 6609.
6. 1,1-Dimethoxy-3-hydroxy-hex-5-yne derivatives (**1**, **4**, **6**–**9**) were prepared in good yields from keto compounds according to Scheme 3. Substrate **5**, **10** were synthesized from commercially available acetylacetaldehyde dimethyl acetal by addition of propargyl magnesium bromide and 1-(trimethylsilyl)-1-propyne lithium salt, respectively. All substrates were fully characterized by ^{1}H, ^{13}C NMR and IR spectroscopy.
7. General procedure for Lewis acid-mediated cyclization reaction: The cyclization reaction was performed by addition of $TiCl_4$ (1.1 equiv. in CH_2Cl_2, 1.0 M)/$SnCl_4$ (1.1 equiv. in CH_2Cl_2, 0.1 M) to the 0.1 M solution of the alkynyl acetals in CH_2Cl_2 at −78°C. The reaction mixture was stirred for 10 min, quenched with a saturated $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous phase was extracted Et_2O (20 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and rotary evaporated. The residue was purified by flash chromatography. Data for **2**: 85% yield; white crystal; mp 112–113°C; IR (neat); 3432, 2928, 1660 cm^{-1}; ^{1}H NMR (500 MHz): δ 1.19–1.33 (m, 2 H), 1.36–1.47 (m, 3 H), 1.52–1.70 (m, 2 H), 1.31 (s, 3 H), 2.02–2.11 (dd, J=6.9, 6.0 Hz, 1 H), 2.17–2.26 (d br t, J=J=18.0, 2.5 Hz, 1 H), 2.47–2.52 (dt, J=18.0, 2.5 Hz, 1 H), 3.37 (s, 3 H), 3.65 (dd, J=9.5, 1.0 Hz, 1 H), 6.00 (t, J=1.0 Hz, 1 H); ^{13}C NMR (125 MHz): δ 21.9, 25.1, 26.0, 39.8, 45.1, 48.6, 57.1, 72.3, 80.5, 125.0, 132.0; HRMS (CI$^+$, NH_3) calcd for $C_{11}H_{16}ClO$ (M-OH)$^+$ 199.0890, found 199.0890; **3**: 87% yield (diastereomeric ratio=1:1). Data for **3a**: colorless oil; IR (neat); 3614, 3447, 1707 cm^{-1}; ^{1}H NMR (400 MHz): δ 1.60–1.74 (m, 3 H), 1.91 (m, 1 H), 1.98 (m, 1 H), 2.17 (m, 1 H), 2.28 (m, 1 H), 2.39 (m, 1 H), 2.47 (ddd, J=9.9, 6.4, 5.0 Hz, 1 H), 3.34 (s, 3 H), 4.13 (dd, J=7.3, 6.4 Hz, 1 H), 4.79 (dd, J=11.0, 6.6 Hz, 2 H), 5.14 (dd, J=7.3, 6.6 Hz, 1 H); ^{13}C NMR (125 MHz): δ 25.1, 28.0, 28.6, 30.4, 42.9, 56.4, 57.5, 76.7, 90.5, 209.2, 211.2. Data for **3b**: colorless oil; IR (neat); 3614, 3447, 1707 cm^{-1}; ^{1}H NMR (400 MHz): δ 1.57–1.69 (m, 3 H), 1.85 (m, 1 H), 1.96–2.07 (m, 2 H), 2.34 (m, 1 H), 2.41 (m, 1 H), 2.56 (ddd, J=10.5, 5.2, 3.6 Hz, 1 H), 3.34 (s, 3 H), 4.10 (dd, J=7.2, 5.2 Hz, 1 H), 4.80 (dd, J=11.0, 8.2 Hz, 2 H), 4.98 (dd, J=8.2, 7.2 Hz, 1 H); ^{13}C NMR (125 MHz): δ 24.8, 28.6, 30.2, 42.6, 56.3, 57.3, 76.3, 79.4, 89.6, 210.1, 211.6; HRMS (CI$^+$, NH_3) calcd for $C_{11}H_{16}O_2$ (M)$^+$ 180.1150, found 180.1153. Data for **11**: 88% yield; white crystal; mp 176–178°C; IR (neat); 3676, 2954, 1660 cm^{-1}; ^{1}H NMR (300 MHz): δ 0.89 (s, 9 H), 1.04–1.09 (m, 2 H), 1.37–1.49 (m, 2 H), 1.61–1.65 (m, 1 H), 1.73–1.79 (m, 1 H), 2.02 (m, 2 H), 2.23–2.29 (d br t, J=17.4, 2.7 Hz, 1 H), 2.44–2.52 (dt, J=17.4, 2.7 Hz, 1 H), 3.37 (s, 3 H), 3.65 (dd, J=9.3, 1.5 Hz, 1 H), 6.01 (t, J=2.4 Hz, 1 H); ^{13}C NMR (125 MHz): δ 22.8, 26.0, 28.3, 33.2, 40.2, 45.5, 47.9, 48.4, 57.0, 71.9, 80.5, 124.9, 132.1; HRMS (CI$^+$, NH_3) calcd for $C_{15}H_{24}ClO$ (M–OH)$^+$ 255.1516, found 255.1513. Data for **12**: 74% yield; colorless oil; IR (neat); 3420, 2969, 2826, 1657 cm^{-1}; ^{1}H NMR (300 MHz): δ 1.35 (s, 3 H), 1.52 (dd, J=12.8, 9.1 Hz, 1 H), 2.11 (dd, J=12.8, 5.9 Hz, 1 H), 2.27–2.34 (dt, J=17.8 Hz, 1 H), 2.48–2.56 (dt, J=17.8 Hz, 1 H), 3.38 (s, 3 H), 4.09 (ddd, J=9.1, 5.9, 2.0 Hz, 1 H), 6.01 (br s, J=2.0 Hz, 1 H); ^{13}C NMR (100 MHz): δ 30.3, 40.0, 46.9, 56.1, 70.9, 74.9, 124.7, 132.0; HRMS (CI$^+$, NH_3) calcd for $C_7H_{10}ClO$ (M–OH)$^+$ 145.0420, found 145.0427. Data for **13**: 68% yield; colorless oil; IR (neat); 3429, 2930, 1654 cm^{-1}; ^{1}H NMR (400 MHz): δ 2.18 (s, 3 H), 2.56–2.61 (dd, J=15.8, 4.9 Hz, 1 H), 2.75–2.81 (dd, J=15.8, 8.0 Hz, 1 H), 3.32 (s, 3 H), 4.18 (ddd, J=8.0, 6.8, 4.9 Hz, 1 H), 4.79–4.87 (dd, J=11.0, 7.0 Hz, 2 H), 5.08



Scheme 3. (a) LDA, TMS-Cl, THF, −78°C for **1**,**4**,**6**,**7**; (b) TMS-Cl, TEA, DMF, 80°C for **8**,**9**; (c) MeLi, $CH(OCH_3)_3$, BF_3-OEt_2, Et_2O, −78°C; (d) propargyl magnesium bromide, Et_2O, 0°C for **1**,**4**–**9**; (e) 1-(trimethylsilyl)-1-propyne, *t*-BuLi, THF, −78°C for **10**.

(dd, $J=7.0$, 6.8 Hz, 1 H); ^{13}C NMR (125 MHz): δ 30.4, 31.6, 50.0, 57.1, 76.3, 77.2, 91.1, 207.0, 209.1; HRMS (CI^+, NH_3) calcd for $C_8H_{13}O_2$ $(M+H)^+$ 141.0915, found 141.0918. Data for **14**: 75% yield; colorless oil; IR (neat); 3439, 2965, 2930, 2829 cm^{-1}; ^{1}H NMR (500 MHz): δ 0.95 (t, 7.5 Hz, 3 H), 1.40–1.44 (dd, $J=13.0$, 9.0 Hz, 1 H), 1.57–1.62 (q, 15.0, 9.5 Hz, 2 H), 2.07–2.11 (dd, $J=13.0$, 6.0 Hz, 1 H), 2.21–2.25 (dt, $J=18.0$ Hz, 1 H), 2.48–2.53 (dt, $J=18.0$ Hz, 1 H), 3.38 (s, 3 H), 4.08–4.13 (ddd, $J=9.0$, 6.0, 2.0 Hz, 1 H), 6.02 (br s, $J=2.0$ Hz, 1 H); ^{13}C NMR (125 MHz): δ 8.0, 36.3, 38.7, 45.5, 56.8, 73.8, 75.7, 125.6, 132.6; HRMS (CI^+, NH_3) calcd for $C_7H_{10}ClO$ $(M)^+$ 190.0761, found 190.0759. Data for **15**: 72% yield; colorless oil; IR (neat); 3450, 2967, 2883, 2826 cm^{-1}; ^{1}H NMR (500 MHz): δ 0.94–0.98 (m, 7.0 Hz, 6 H), 1.38–1.41 (dd, $J=14.0$, 7.0 Hz, 1 H), 1.69–1.72 (m, 7.0 Hz, 1 H), 2.08–2.12 (dd, $J=13.0$, 6.0 Hz, 1 H), 2.14–2.18 (dt, $J=18.0$ Hz, 1 H), 2.50–2.55 (dt, $J=18.0$ Hz, 1 H), 3.39 (s, 3 H), 4.09–4.12 (ddd, $J=8.0$, 5.5, 2.0 Hz, 1 H), 6.02 (br s, $J=2.0$ Hz, 1 H); ^{13}C NMR (125 MHz): δ 17.2, 17.3, 37.0, 38.9, 43.0, 56.8, 75.9, 125.7, 132.7; HRMS (CI^+, NH_3) calcd for $C_7H_{10}ClO$ $(M–OH)^+$ 204.0917, found 204.0916. Data for **16**: 70% yield; colorless oil; IR (neat); 3447, 2977, 2825, 1664 cm^{-1}; ^{1}H NMR (300 MHz): δ 1.06 (d, $J=6.6$ Hz, 3 H), 1.28 (s, 3 H), 1.48–1.63 (dd, $J=9.0$, 6.6 Hz, 1 H), 2.30–2.36 (d br t, $J=17.7$, 2.7 Hz, 1 H), 2.51–2.59 (dt, $J=17.7$, 2.7 Hz, 1 H), 3.39 (s, 3 H), 3.62 (ddd, $J=9.0$, 2.7, 2.4 Hz, 1 H), 6.01 (t, $J=2.4$ Hz, 1 H); ^{13}C NMR (125 MHz): δ 11.1, 28.5, 42.5, 48.3, 57.0, 73.3, 81.2, 124.7, 132.3. Data for **17**: 67% yield; colorless oil; IR (neat); 3362, 2973, 2897, 1659 cm^{-1}; ^{1}H NMR (300 MHz): δ 0.85 (d, $J=6.9$ Hz, 3 H), 1.31 (s, 3 H), 2.02–2.11 (dd, $J=6.9$, 6.0 Hz, 1 H), 2.17–2.26 (d br t, $J=17.8$, 2.6 Hz, 1 H), 2.46–2.54 (dt, $J=17.8$, 2.6 Hz, 1 H), 3.38 (s, 3 H), 4.17 (ddd, $J=6.0$, 2.6, 1.1 Hz, 1 H), 5.85 (t, $J=1.1$ Hz, 1 H); ^{13}C NMR (125 MHz): δ 11.2, 28.1, 40.3, 49.4, 71.0, 74.0, 127.1, 134.2; HRMS (CI^+, NH_3) calcd for $C_9H_{14}ClO$ $(M–OH)^+$ 173.0733, found 173.0737.

8. The axial orientation of the hydroxy group at C1 of **2** was confirmed by the existence of NOE between H_a, H_e and OH at C1. The key interactions are illustrated here: