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Ti(III)-mediated opening of 2,3-epoxy alcohols to build five-membered carbocycles with multiple chiral centres ☆

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ABSTRACT

Stereoselective construction of highly substituted five-membered carbocycles with multiple chiral centres is described. Sharpless kinetic resolution was applied as the key step to prepare the required 2,3-epoxy alcohols and a Ti(III) radical mediated opening of the epoxide ring followed by intramolecular trapping of the generated radical with a suitably placed α,β-unsaturated ester resulted in the formation of five-membered carbocycles with up to three consecutive new chiral centres stereoselectively fixed.

Stereoselective C–C bond forming reaction based on free radicals is a challenging task and an attractive scenario in the synthetic organic community.[1] $Cp_2Ti(III)Cl$ mediated reactions[2] play a significant role in organic synthesis and for the last few years we have been working extensively on the Ti(III) radical mediated epoxide opening reactions. To our delight, chiral 1,3-diols[3a, 3b] (**2**) and quaternary chiral centres[3c] (**3**) were obtained from epoxy alcohols (**1**) upon treatment with Ti(III) radical, whereas highly functionalized carbocycles[3c]/oxacycles[3d]/azacycles[3e] (**5**) were delivered from compound **4** (Scheme 1). Successful application of this Ti(III) mediated radical transformation for synthetic studies of several biologically active natural products has already been demonstrated by us.[4]

With the success obtained from our previous studies,[3,4] we were interested in investigating Ti(III) radical mediated epoxide opening reaction for construction of highly functionalized five-membered carbocycles.[5] Cyclopentanoid motif is an important and integral part of many biologically active natural products. Earlier we have shown that functionalized six-membered carbocycles[3c] can be synthesized from chiral 2,3-epoxy alcohol (**4**, X = CH_2; n = 2). Thus conceptually five-membered carbocycles can be synthesized from 2,3-epoxy alcohols **6A–D** via a similar sort of Ti(III) mediated reaction and the products can be further manipulated to get the natural products like[6] coronatine (**8**), (+)-*epi*-jasmonic acid (**9a**), tuberonic acid (**9b**), β-D-glucopyranosyltuberonic acid (**9c**) and the biosynthetic precursors 12-oxo-PDA (**10a**), OPC 8:0 (**10b**). Presence of trisubstituted unsaturation as shown in **6B,D** can provide five-membered carbocycles with additional methyl centre at the side arm so that some iridoids[7] like nepetalactone (**11**), iridomyrmecin (**12**), δ-skytanthine (**13**) can be synthesized (Fig. 1). In this Letter we wish to report the Ti(III) radical mediated opening of 2,3-epoxy alcohols **6A–D** to construct five-membered carbocycles **7A–D** with multiple chiral centres.

In a similar approach as that of our previous studies,[3] we have envisioned that various 2,3-epoxy alcohols **6A–D** with in-built α,β-unsaturation are the suitable candidates for making five-membered carbocycles via a Ti(III) mediated epoxide opening reaction. These epoxy alcohols can be prepared by applying Sharpless' kinetic resolution[8] method over the racemic allylic alcohols **14A–D**, which in turn could be obtained by successive Wittig olefination[9] and desilylation of the aldehydes **15a–b**. The required aldehydes **15a–b** can be obtained from the alkynol **16** (Scheme 2).

We started our synthesis from the commercially available pent-4-yn-1-ol (**16**) which was protected as its PMB ether using PMBBr and NaH by applying known[10] procedure to get compound **17** in 95% yield (Scheme 3). Treatment of the acetylide,[11] generated from compound **17** by using ^{n}BuLi, with aldehydes **18a–b** resulted in the formation of propargyl alcohols **19a–b** in excellent yield.

Reaction of compounds **19a–b** with Red-Al[12] produced the allylic alcohols **20a–b** which were protected using TBSOTf and

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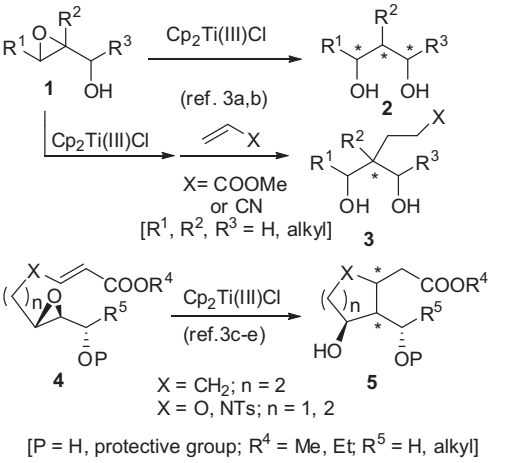
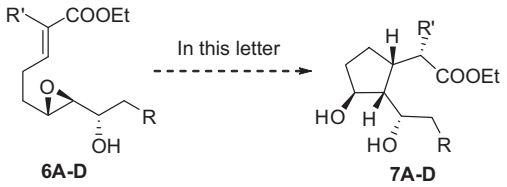
2,6-lutidine to get the TBS ethers **21a–b** in good yield. Oxidative cleavage of PMB ether functionality was carried out by employing DDQ under buffered conditions[13] to get the primary alcohols **22a–b** which were oxidized to the corresponding aldehydes **15a–b** under Swern oxidation[14] conditions.

Reaction of the aldehydes **15a–b** with stabilized[9] phosphoranes $Ph_3PC(R')COOEt$ (R′=H, CH_3) produced the α,β-unsaturated esters **23A–D,** which were desilylated using TBAF to get the allylic alcohols **14A–D** (Scheme 4). Sharpless kinetic resolution (SKR)[8] of the racemic compounds **14A–D** resulted in the formation of 2,3-epoxy alcohols **6A–D** in appropriate yields. To our pleasure, unreacted allylic alcohols **24A–D** could be converted back to the precursor allylic alcohols **14A–D** via a two step sequence that is Swern oxidation[14] and Luche reduction conditions.[15]

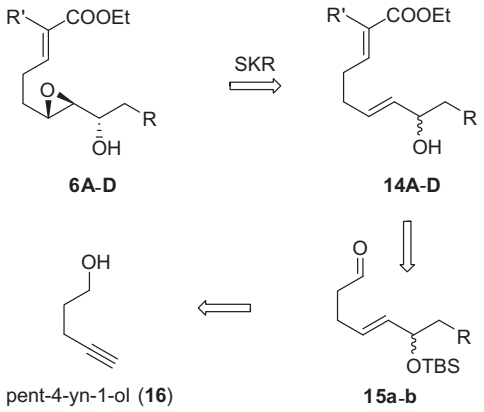
Now the stage was set to carry out the crucial $Cp_2Ti(III)Cl$ radical mediated epoxide ring opening reaction. Reaction of the epoxy





A: R = H, R'= H; **B**: R = H, R' = CH_3;
C: R = OBn, R' = H; **D**: R = OBn, R' = CH_3;

Scheme 1. Synthesis of chiral 1,3-diols, quaternary chiral centres, carbocycles, oxacycles and azacycles.



a: R = H; **b**: R = OBn;
A: R = H, R'= H; **B**: R = H, R' = CH_3;
C: R = OBn, R' = H; **D**: R = OBn, R' = CH_3;

Scheme 2. Retrosynthetic analysis of 2,3-epoxy alcohols **6A–D**.

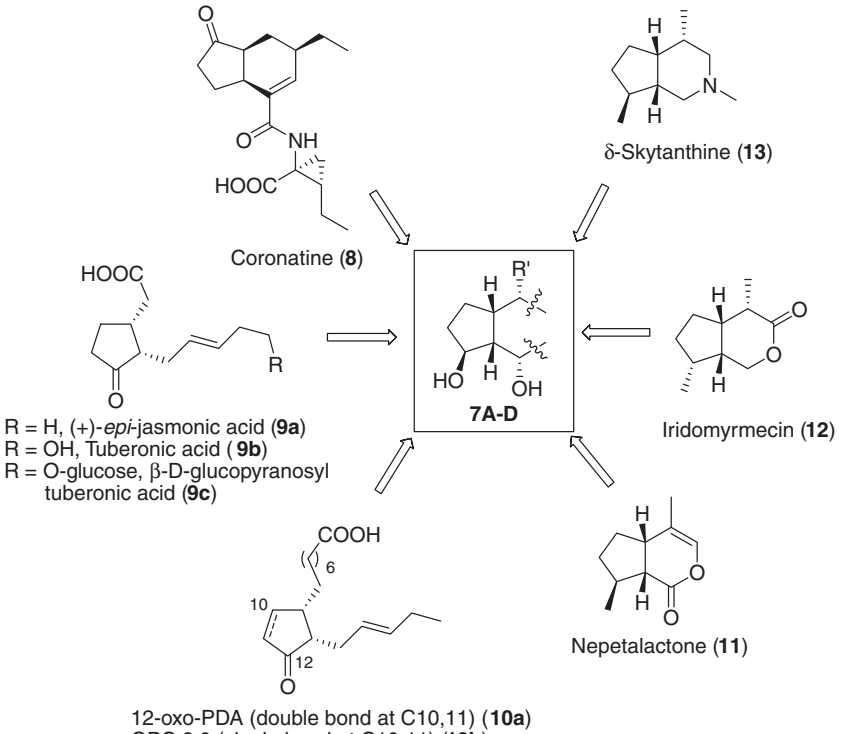
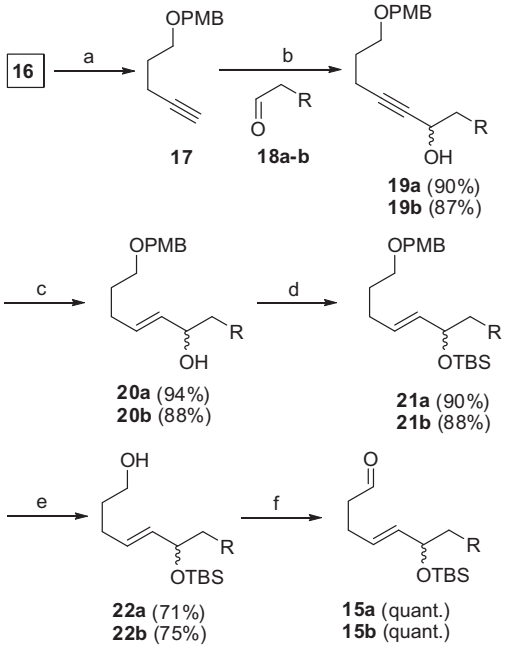
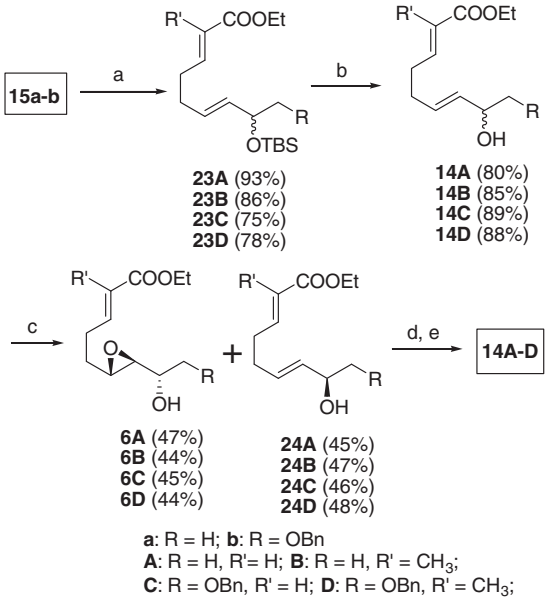


Figure 1. Schematic representation of the possible uses of intermediates **7A–D** prepared by our method in the syntheses of various natural products.



Scheme 3. Synthesis of aldehydes **15a–b**. Reagents and conditions: (a) PMBBr, NaH, TBAI, THF, 0 °C–rt, 12 h, 95%; (b) ^{n}BuLi, −78 °C, 30 min, RCH_2CHO, 10 min, −78 °C; (c) Red-Al, Et_2O, 0 °C–rt, 4 h; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min; (e) DDQ, $CHCl_3$/phosphate buffer (pH 7, 20:1), rt, 10 min; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, quant.



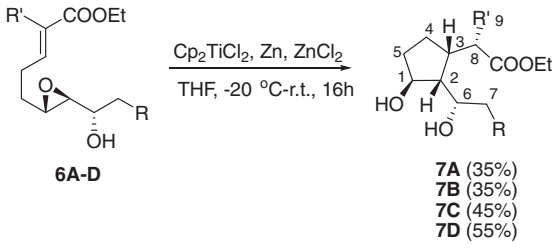
Scheme 4. Synthesis of 2,3-epoxy alcohols **6A–D**. Reagents and conditions: (a) $Ph_3PC(R')COOEt$, CH_2Cl_2, rt, overnight; (b) TBAF, THF, 0 °C–rt, 6 h; (c) 4 Å MS, $Ti(O^iPr)_4$, *L*-(+)-DIPT, TBHP, CH_2Cl_2, −20 °C, 2 h; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, quant.; (e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C–rt 1.5 h, 75–80%.

alcohols **6A–D** with $Cp_2Ti(III)Cl$ radical, which was generated[16] in situ by the reaction of Cp_2TiCl_2, Zn, and fused $ZnCl_2$, produced a radical that underwent smooth intramolecular cyclization with α,β-unsaturation, thereby forming a new C–C bond and led to highly functionalized five-membered carbocycles **7A–D** as the major isolable products (Scheme 5).[17]

The relative stereochemistry of C2, C3 (**7A–D**), and C8 (**7B,D**) centres was unequivocally assigned by incisive NMR studies[18a] such as NOESY and HSQC experiments. These compounds have been analyzed by using 1D–1H decoupling and 2D NMR techniques, such as DQF-COSY and NOESY. The conformation of the molecule is fixed by considering the observed coupling constants and NOEs.

We have observed[18b] a consistency in NOE correlations for all of the products **7A–D**. Strong NOE cross-peaks $C_2H \leftrightarrow C_8H_a$ and H_b, $C_2H \leftrightarrow C_7H$, $C_6H \leftrightarrow C_8H_a$ and $C_1H \leftrightarrow C_7H$ were observed for the compounds **7A–D**. In addition to these observations, strong NOE correlation $C_3H \leftrightarrow C_9H$ was also observed in compounds **7B,D** (Fig. 2). Interestingly, the fixation of C8 methyl stereo centre was found to be the same in both **7B** and **7D**.

In conclusion, we have synthesized highly functionalized five-membered carbocycles with multiple chiral centres by applying $Cp_2Ti(III)Cl$ radical mediated ring opening of 2,3-epoxy alcohols followed by intramolecular trapping of the radical with suitably placed α,β-unsaturation. That three consecutive chiral centres



Scheme 5. Ti(III) radical mediated opening of 2,3-epoxy alcohols.

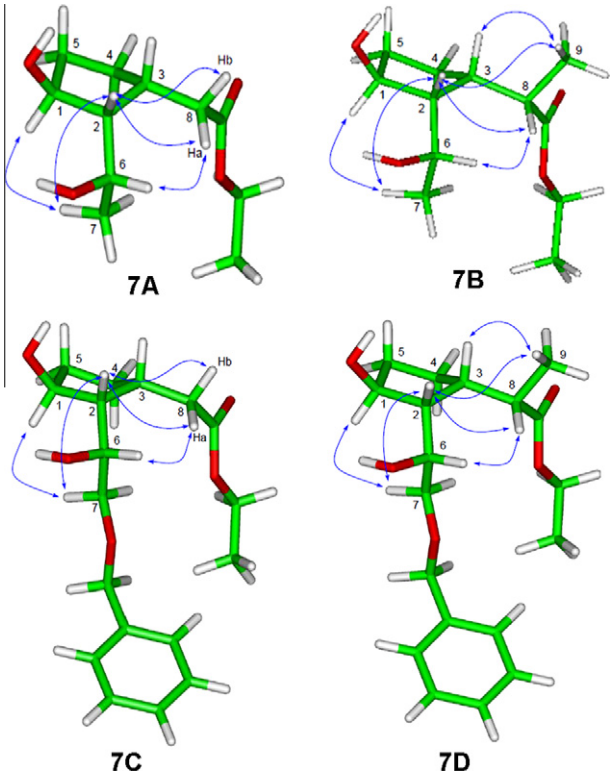


Figure 2. Energy minimized structures of **7A–D** with the observed strong NOESY relations (blue arrows).

were fixed in a single-step radical mediated reaction is noteworthy. Further studies are underway in the laboratory in order to extend this work for the application in the synthesis of natural products and will be reported in due course.

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16. *Generalized experimental procedure for Ti(III) radical mediated epoxide opening reaction*: Activated Zn powder (6 equiv), freshly fused $ZnCl_2$ (3 equiv) and Cp_2TiCl_2 (3 equiv) were taken in anhydrous THF (15 mL/mmol of substrate) and stirred for 30 min at room temperature. The color of the reaction mixture turned into deep green from deep red. Then it was cooled to −20 °C and a solution of 2,3-epoxy alcohol **6A–D** (1 equiv) in anhydrous THF was introduced via cannula. The reaction mixture was then slowly allowed to attain room temperature over a period of 2 h and stirred for additional 14 h before it was quenched with 1 N HCl and then extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, water, saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by using standard silica gel column chromatography (22–28% ethyl acetate in petroleum ether eluant) afforded the five-membered carbocycles **7A–D**.
17. *Analytical and spectral data of five-membered carbocycles. Compound* **7A**: R_f = 0.3 (silica gel, 40% ethyl acetate in hexane); $[\alpha]_D^{24}$ = +28.1 (*c* 1.43, $CHCl_3$); IR (neat): ν_{max} 3357 (br), 2963, 2924, 1729, 1372, 1298, 1256, 1171, 1115, 1030, 952 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.52 (td, *J* = 4.7,1.5 Hz, 1H, C_1H), 4.14 (q, *J* = 7.2 Hz, 2H, $COOCH_2CH_3$), 3.97 (qd, *J* = 6.5, 4 Hz, 1H, C_6H), 2.61 (m, 1H, C_3H), 2.40 (dd, *J* = 16, 6.5 Hz, 1H, C_8H_b), 2.34 (dd, *J* = 16, 7.3 Hz, 1H, C_8H_α), 2.13 (m, 1H, C_4H_β), 1.8 (m, 1H, C_5H_α), 1.67 (m, 1H, C_5H_β), 1.37 (d, *J* = 6.5 Hz, 3H, C_7H_3), 1.34 (m, 1H, C_4H_α), 1.32 (dt, *J* = 10.3, 4.3 Hz, 1H, C_2H), 1.26 (t, *J* = 7.2 Hz, 3H, $COOCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 74.7, 66.8, 60.6, 56.1, 38.8, 34.0, 33.4, 29.3, 21.9, 14.2; ESI-MS: *m*/*z* (%) 217 (95) $[M+H]^+$, 239 (100) $[M+Na]^+$; HRMS (ESI): calcd for $C_{11}H_{20}O_4Na$ $[M+Na]^+$ 239.1259, found 239.1265; *Compound* **7B**: R_f = 0.3 (silica gel, 50% ethyl acetate in hexane); $[\alpha]_D^{24}$ = +26.3 (*c* 0.95, $CHCl_3$); IR (neat): ν_{max} 3358 (br), 2969, 2934, 1728, 1452, 1376, 1254, 1180, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.53 (td, *J* = 4.6, 2.3 Hz, 1H, C_1H), 4.12 (q, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 4.0 (qd, *J* = 6.4, 4 Hz, 1H, C_6H), 2.61 (qd, *J* = 7.1, 4.8 Hz, 1H, C_8H), 2.54 (m, 1H, C_3H), 1.99 (m, 1H, C_4H_β), 1.72 (m, 1H, C_5H_α), 1.64 (m, 1H, C_5H_β), 1.56 (dt, *J* = 8.8, 4.4 Hz, 1H, C_2H), 1.51 (m, 1H, C_4H_α), 1.37 (d, *J* = 6.5 Hz, 3H, C_7H_3), 1.2 (t, *J* = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.17 (d, *J* = 7 Hz, 3H, C_9H_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 75.2, 67.5, 60.3, 51.9, 40.9, 40.0, 33.6, 25.7, 22.3, 14.7, 14.3; ESI-MS: *m*/*z* (%) 231 (100) $[M+H]^+$, 253 (50) $[M+Na]^+$; HRMS (ESI): calcd for $C_{12}H_{22}O_4Na$ $[M+Na]^+$ 253.1415, found 253.1427; *Compound* **7C**: R_f = 0.4 (silica gel, 60% ethyl acetate in hexane); $[\alpha]_D^{24}$ = +20.7 (*c* 0.41, $CHCl_3$); IR (neat): ν_{max} 3391 (br), 2926, 1721, 1652, 1256, 1105, 1038, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.20 (m, 5H, Ar*H*), 4.52 (s, 2H, $PhCH_2$), 4.35 (td, *J* = 5.3, 2.5 Hz, 1H, C_1H), 4.03 (q, *J* = 7.4 Hz, 2H, $COOCH_2CH_3$), 3.96 (m, 1H, C_6H), 3.6 (d, *J* = 5 Hz, 2H, C_7H_2), 2.56 (m, 1H, C_3H), 2.35 (dd, *J* = 15.4, 5.4 Hz, 1H, C_8H_b), 2.17 (dd, *J* = 15.4, 8.5 Hz, 1H, C_8H_a), 2.05 (m, 1H, C_4H_β), 1.76 (m, 1H, C_5H_α), 1.58 (m, 1H, C_5H_β), 1.46 (dt, *J* = 9.7, 4.8 Hz, 1H, C_2H), 1.24 (m, 1H, C_4H_α), 1.15 (t, *J* = 7.4 Hz, 3H, $COOCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 137.7, 128.6, 127.9, 127.8, 74.9, 73.8, 70.6, 70.3, 60.4, 51.6, 38.9, 34.9, 33.6, 29.0, 14.2; ESI-MS: *m*/*z* (%) 323 (70) $[M+H]^+$, 340 (20) $[M+NH_4]^+$, 345 (100) $[M+Na]^+$; HRMS (ESI): calcd for $C_{18}H_{26}O_5Na$ $[M+Na]^+$ 345.1677, found 345.1669; *Compound* **7D**: R_f = 0.5 (silica gel, 50% ethyl acetate in hexane); $[\alpha]_D^{24}$ = +28.9 (*c* 0.84, $CHCl_3$); IR (neat): ν_{max} 3391 (br), 2930, 1720, 1452, 1264, 1176, 1100, 1041, 740, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H, Ar*H*), 4.52 (s, 2H, $PhCH_2$), 4.35 (td, *J* = 5.1, 2.6 Hz, 1H, C_1H), 4.03 (q, *J* = 7.2 Hz, 2H, $COOCH_2CH_3$), 4.00 (m, 1H, C_6H), 3.6 (d, *J* = 5.4 Hz, 2H, C_7H_2), 2.56 (qd, *J* = 7.2, 5.09 Hz, 1H, C_8H), 2.44 (m, 1H, C_3H), 1.92 (m, 1H, C_4H_β), 1.69 (m, 1H, C_2H), 1.66 (m, 1H, C_5H_α), 1.58 (m, 1H, C_5H_β), 1.42 (m, 1H, C_4H_α), 1.15 (t, *J* = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.1 (d, *J* = 7.1 Hz, 3H, C_9H_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 137.6, 128.5, 127.9, 127.8, 75.3, 74.0, 73.6, 70.8, 60.2, 48.3, 41.3, 41.0, 33.6, 25.3, 15.5, 14.3; ESI-MS: *m*/*z* (%) 337 (100) $[M+H]^+$, 359 (95) $[M+Na]^+$; HRMS (ESI): calcd for $C_{19}H_{28}O_5Na$ $[M+Na]^+$ 359.1834, found 359.1820.
18. (a) Jeener, J.; Meier, B. H.; Bachmann, P.; Ernst, R. R. *J. Chem. Phys.* **1979**, *71*, 4546–4553; (b) Consistent pattern of a cis-junction has been observed in the formation of five-membered targets and a trans-junction in six-membered targets during our previous Ti(III) mediated epoxide opening reactions. See: Refs. 3c–e and 4a.