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HIGHLY FUNCTIONALIZED FIVE-MEMBERED BICYCLIC α -HYDROXY ACIDS FROM SYNTHETIC EQUIVALENT OF GLYCOLIC ACIDS

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ABSTRACT

*Five-membered cyclic α -hydroxy acids (1-hydroxycycloalkane-1-carboxylic acids) are important constituents in biologically active natural products and also important precursor molecules for the synthesis of pharmacologically active compounds. This paper presents stereo selective synthesis of polysubstituted five-membered bicyclic α -hydroxy acid derivatives from α, α -dialkylated 1,3-dioxolan-4-one (**9**). The synthesis was initiated on the α -propagation of 2-(tert-butyl)-5-(1-ethenylprop-2-enyl)-1, 3-dioxololan-4-one (**trans-8**) via its enolate, followed by intramolecular Pauson-Khand cyclization. The reaction was stereo selective and afforded two isomers (**10a** and **10b**) in 4:1 ratio out of four possible diastereoisomers of bicyclic α -hydroxy acid (bicyclic 1-hydroxycarboxylic acid) derivatives. This method opens a new avenue to prepare synthetically useful highly functionalized stereoselective synthesis of five-membered bicyclic α -hydroxy acids using a convenient and very effective method.*

Keywords: Stereoselective synthesis, glycolic acids, five-membered bicyclic α -hydroxy acids, Pauson - Khand reaction,

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1.0 INTRODUCTION

Cyclic α -hydroxy carboxylic acids are important constituents in pharmacological active natural products and important synthetic building units for the synthesis of various biologically active natural products [1]. Although the research has mainly focused on the development of potential synthetic strategies for the synthesis of acyclic α -hydroxy acids [2], less attention has been paid on preparation of cyclic α -hydroxy acids. Glycolic acids is an easily available, important α -hydroxy acid which can be easily converted into the asymmetric acetals, and then it can serve as chiral auxiliaries in selective induction of its α -position to prepare asymmetric 1-hydroxycycloalkane-1-carboxylic acid derivatives [3]. In our previous work, we reported stereo selective preparation of 1-hydroxycyclopentene-1-carboxylic acid derivatives (**3**, **Figure 1**) using chiral equivalent of glycolate derivatives via metathesis. This method has been successfully applied in the synthesis of natural product, (-)-quinic acid [4]. In another method, we have demonstrated synthesis of polysubstituted 1-hydroxycyclopentane-1-carboxylic acid derivatives (**6a** and **6b**, **Figure 2**) using chiral equivalent of glycolate derivatives via a group selective radical annulation procedure [5].

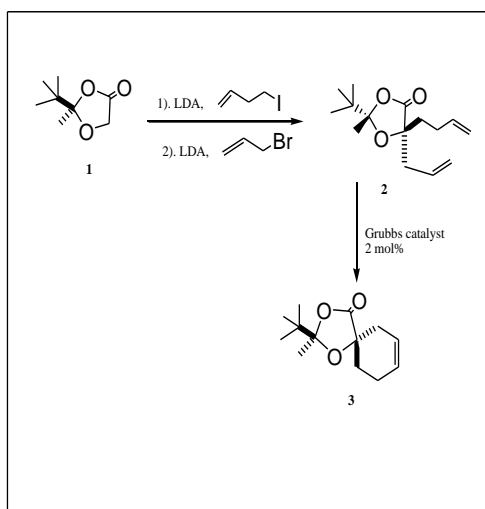


Figure 1: Synthesis of 1-hydroxycycloalkene-1-carboxylic acid by Metathesis

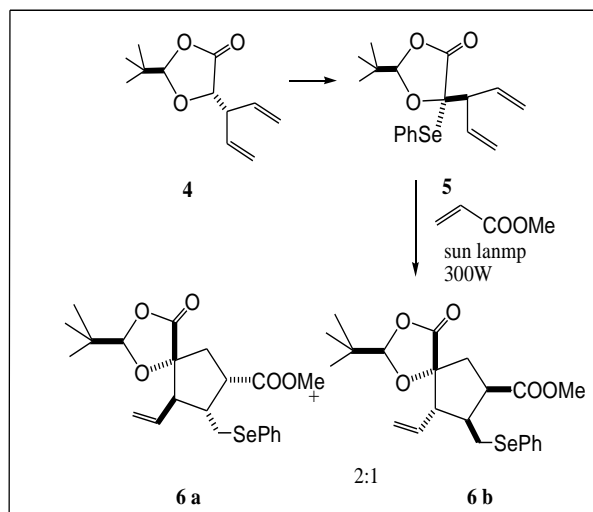


Figure 2: Synthesis of 1-hydroxycycloalkene-1-carboxylic acid via radical annulation

Development of synthetic strategies for the preparation of asymmetric bicyclic α -hydroxy acids is equally important in organic synthesis. Pauson-Khand reaction has emerged as a convenient tool for the synthesis of cyclopentenones, from alkynes and alkene, involving of cobalt carbonyl compounds [6]. In this reaction, the alkyne first reacts with $\text{Co}(\text{CO})_8$ to form alkyne- $\text{Co}_2(\text{CO})_6$ complex and then it reacts with the alkene to form the cyclopentanone. We have planned a synthetic route to bicyclic 1-hydroxycarboxylic acid derivatives based on intramolecular Pauson-Khand cyclization of α,α -dialkylated glycolic acid derivatives. As a demonstration of the proposed method, we explain here the synthesis of asymmetric polysubstituted bicyclic 1-hydroxycarboxylic acids (**10a and 10b**, **Figure-5**) using glycolate derivatives synthesized via simple reactions process (**Figure 3 & 4**).

2.0 MATERIAL AND METHOD

2.1 General material and instruments used

All the chemicals were purchased from Fluka, Switzerland. THF was freshly distilled in the presence of K under N_2 , CH_2Cl_2 was distilled in the presence of CaH_2 under N_2 . Other reagents were obtained from commercial sources. For flash column chromatography: Merck silica gel 60 (70-230 mesh) and for TLC: Merck silica gel 25 F₂₅₄, analytical plates were used. Detection either by UV, I_2 or by spraying with phosphomolybdic acid solution, Diastereoselectivity was determined by means of GC; column Machenery-Nagel-OPTIMA-1701. Melting point was determined by Reicher Thermovar Kofler. IR spectra: Perkin-Elmermattson Unicam 50016PC FT-IR; NMR spectra: Varian Gemini 200 (^1H =200 MHz, ^{13}C -50.3 MHz); Bruker AM 360 (^1H =360 MHz, ^{13}C = 90.5 MHz); Bruker Advance DRX 500 (^1H =500.13 MHz, ^{13}C =125.8 MHz), chemical shift in ppm relative to tetramethylsilane ($\delta = 0$); CDCl_3 ($\delta = 7.26$ ppm) used as the solvent unless otherwise stated; Mass: *Vaccum Generators Micromass* VG70/70E; DS 11-250; EI (70 eV); CI (CH_4); m/z (%); FAB: matrix in 2-nitrobenzylalcohol with Ar at 8 kV; IR in cm^{-1} ; Elemental analysis: Ilse Beetz, Microanalytisches Laboratorium, D-8640 Kronach, Germany.

2.2 Method

The initial compound, ethyl 3-ethenyl-2-hydroxypent-4-enoate (**7**) to be used in the synthesis of precursor molecule for the targeted Pauson–Khand reaction, was prepared by the reaction of 5-bromo-1,3-pentadiene with ethyl glyoxylate with the presence of Zn powder and anhydrous AlCl_3 (**Figure 3**) [7], [8]. This compound was then reacted with pivalaldehyde in the presence of acid catalyst to obtain 2-(*tert*-butyl)-5-(1-ethenyl prop-2-enyl)-1,3-dioxolane-4-one (**8**, **Figure 3**) [4]. The *trans* isomer of **8** (α -monosubstituted cyclic acetal of glycolate) which was obtained through column chromatographic purification of the mixture, was deprotonated with LDA in THF at -78°C and then followed by alkylation with propargyl bromide to form α -disubstituted cyclic acetal of glycolate (**9**, **Figure 4**), which was the substrate for the targeted Pauson-Khand cyclization.

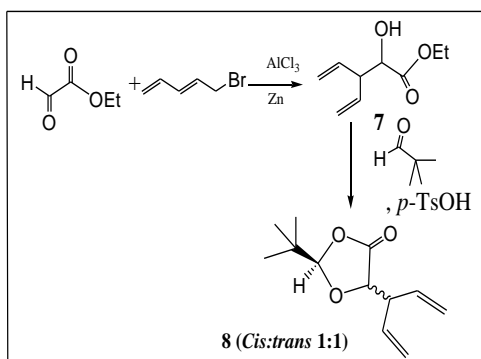


Figure 3 : Preparation of α -monosubstituted cyclic acetal 2-(*tert*-butyl)-5-(1-ethenyl prop-2-enyl)-1,3-dioxolane-4-one

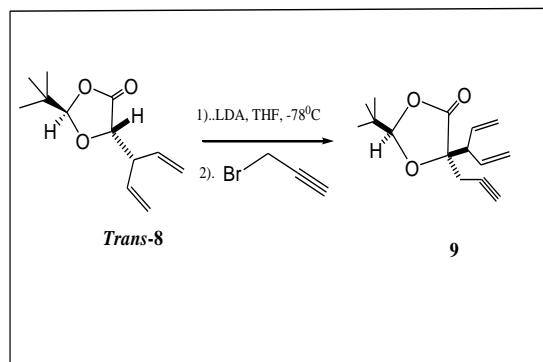


Figure 4 : Preparation of α -disubstituted cyclic acetal, 2-acetal 2-(*tert*-butyl)-5-(2-propynyl)-5-(1-vinyl-2-propenyl)-1,3-dioxolane-4-one

At the next step, the compound **9** (2-*tert*-butyl-5-(2-propenyl)-5(1-vinyl-2-propenyl)-1,3-dioxolane-4-one) was subjected to the intramolecular Pauson–Khand cyclization by reacting with cobalt carbonyl, $\text{Co}_2(\text{CO})_8$ at room temperature (r.t) followed by separation of the resultant alkyne- $\text{Co}_2(\text{CO})_6$ complex using flash chromatography, and then treating this complex with hydrated N-methylmorpholine-N-oxide (NMO. H_2O) in CH_2Cl_2 at r.t to form the desired bicyclic 1-hydroxycyclopropanecarboxylic acid derivatives (**Figure 5, 10a and 10b,**) [9].

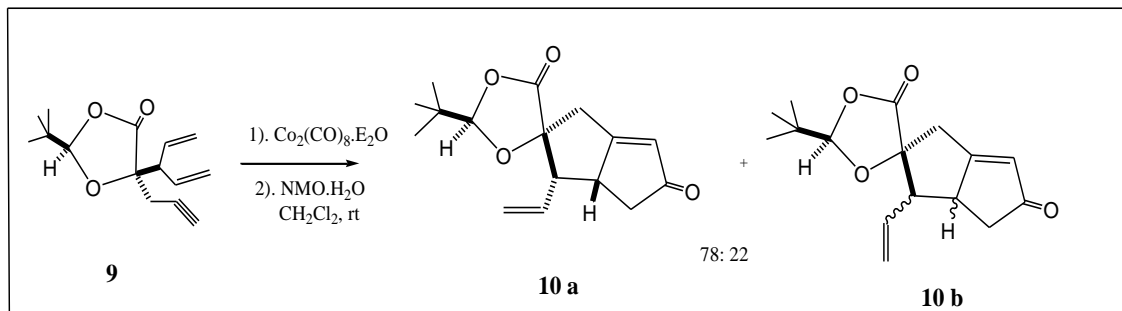


Figure 5: Intramolecular Pauson –Khand reaction to prepare bicyclic α -hydroxyl acid derivatives

The stereo selectivity of the formed mixture of bicyclic 1-hydroxycarboxylic acid derivatives was analyzed with the help of gas chromatography and NMR spectroscopy. The mixture of isomers was separated using preparative HPLC and the structures of the diastereomers along with their relative stereochemistry were determined with the help of NMR studies (NOE difference spectra).

3.0 RESULTS AND DISCUSSION

The formation of ethyl 3-ethenyl-2-hydroxypent-4-enoate (7) was not stereo selective and it was formed as a racemic mixture in 52 % yield in the reaction of nucleophilic addition of 5-bromo-1,3-pentadine to aldehyde carbonyl of ethyl glyoxylate in the presence of AlCl_3 (**Figure 3**). The cyclic acetal (8), 2-(*tert*-butyl)-5-(1-ethenyl prop-2-enyl)-1,3-dioxololan-4-one was formed as a 1:1 (*cis:trans*) mixture in 65 % yield (Figure 3) and two isomers were successfully separable through column chromatography. The alkylation of the *trans* isomer of cyclic acetal, 8 with propargyl bromide was totally selective and afforded 2-(*tert*-butyl)-5-(2-propynyl)-5-(1-vinyl-2-propenyl)-1,3-dioxololan-4-one (9) in 65 % yield (**Figure 4**). The total stereo selectivity in propargylation can be explained using the model given below (**Figure 6**). The enolate derived from the compound 8 should be in the preferable conformation as depicted in the Figure 6 and two vinyl groups are oriented in the way shielding of the two faces of the enolate equally and the propargylation is taken place *anti* to the *tert*-butyl group forming exclusively compound 9 [4], [10]. All the efforts made to alkylate the *cis* isomer were failed giving still no clear reasons.

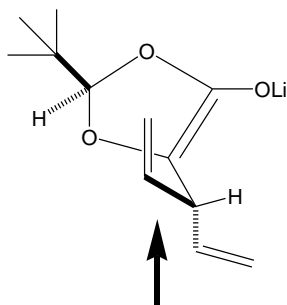


Figure 6: Stereo chemical model for the alkylation of Li-enolate derived from *trans*-8.

Pauson-Khand cyclization of the substrate compound 9 was highly selective and the desired bicyclic 1-hydroxycarboxylic acid derivatives (**Figure 5, 10a and 10b**) were formed as a mixture of two diastereomers (4:1) out of four possible diastereomers. This isomeric mixture could be separable only in preparative HPLC. The NOE different spectra supported to determine the relative stereochemistry of the major isomer, 7-[2-*tert*-butyl]-6-vinyl-1,3'-dioxolan-4-onyl]-bicyclo [3.3.0] oct-1-en-3-one (10a) as shown below (**Figure 7**).

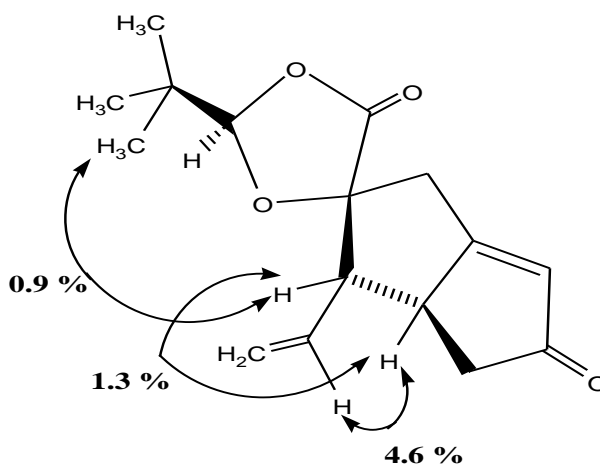


Figure 7: NOE's of major isomer, 10 a

The proposed mechanism for the intramolecular cyclization is given below (**Figure 8**). The stereo chemical outcome of the intramolecular Pauson-Khand cyclization could be rationalized by the formation of pseudo chair conformation of Cobalt-alkyne complex (**A**) with the orientation of one vinyl group at the equatorial position. The cyclization is mainly controlled by steric factors of *tert*-butyl group and *cis*-fused conformation is

dominated with minimizing steric interactions between the vinyl group and the *tert*-butyl group in the intermediate. The metalacycle, **B** then undergo carbonyl insertion to form the intermediate **C**, which is set up to migrate C-Co bond to the adjacent electrophilic carbonyl carbon to form **D**. The reductive elimination of cobalt carbonyl residue ($\text{Co}_2(\text{CO})_5$) of **D** leads to form the major diastereoisomer of **10a**.

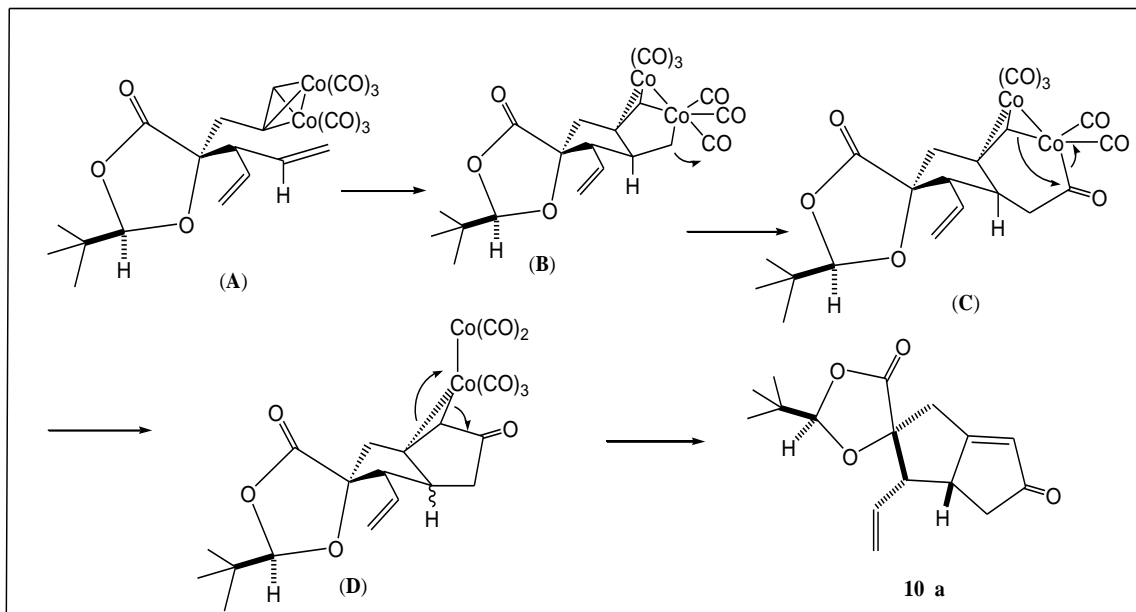


Figure 8: Proposed mechanism for intramolecular Pauson-Khand reaction

4.0 CONCLUSION

We have documented here highly functionalized stereo selective and efficient synthesis of five-membered bicyclic 1- hydroxycarboxylic acid derivatives based on Pauson-Khand cyclization. As 1-hydroxycycloalkane-1-carboxylic acids serve as important starting compounds for the preparation of biologically active molecules, this method can be applied in the synthesis of wide range of biologically relevant molecules.

5.0 ACKNOWLEDGEMENT

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7.0 APPENDIX

7.1 Detail experimental part and spectroscopic data of the compounds

Ethyl 3-ethenyl-2-hydroxypent-4-enoate (7): A solution of 5-bromopenta-1,3-diene (2.0 g, 13.6 mmol) in THF (5 ml) was added to a suspension of Zn (890 mg, 13.6 mmol) and AlCl₃ (1.8 g, 13.6 mmol) in THF (32 ml) at room temperature under N₂. After stirring for 15 min, a solution of ethyl glyoxylate (1.38 g, 13.86 mmol) in THF (5.0 ml) was added and the mixture was stirred for 8 hrs until all starting compound was consumed. Then the mixture was poured into sat. NH₄Cl solution (10.0 ml) and extracted with Et₂O (3 x 40 ml). The combined organic phase was washed with brine, dried with MgSO₄ and evaporated, and crude product was purified by FC (hexane/AcOEt 4:1); compound **7** afforded pale yellow oil, 1.20 g, 52 % yield. IR (Film): 3501, 3080, 2982, 2937, 2936, 1737, 1250, 1109. ¹H-NMR (360 MHz): δ = 5.78-5.71 (m, 2H, 2CH=CH₂); 5.11-4.95 (m, 4H, 2CH=CH₂); 4.2(m, 3H, CHOH, MeCH₂O); 4.15(d, 1H, OH); 3.68-3.51(m, 1H, CH(CH-CH₂)₂); 1.27(t, 3H, MeCH₂O). ¹³C-NMR(50.3MHz); 173.42(s); 136.48(s); 111.91(s); 80.54(s); 61.59(s); 41.5(s),14.2(s). CI-MS: 171(4, {M+1}⁺), 170(36, M⁺), 152(11), 151(5), 142(3), 124(14), 123(8), 122(5), 106(10), 102(6), 96(35), 80(12), 78(30), 77(7), 68(27), 67(54), 66(100), 54(24), Anal. Cal. for C₉H₁₄O₃(170.21): C 63.51, H 8.29; Found C 62.95, H 7.99.

2-(tert-butyl)-5-(1-ethenylprop-2-enyl)-1,3-dioxolane-4-one (8): A mixture of **7** (2.0 g, 11.6 mmol), 2,2-dimethylpropanal (4.0 g, 94.08 mmol), TsOH (950 mg), and 1 drop of conc. H₂SO₄ in pentane (20 ml) was heated under reflux with azeotropic removal of H₂O. After completion of the reaction, the solution was washed with H₂O, dried with MgSO₄ and evaporated under *vacuum*. The crude product was purified by FC (pentane: Et₂O 20:1) gave *cis:trans* mixture of **8** in 1:1 (1.60 g, 65 %). IR (Film): 3583, 3084, 2976, 2910, 2876, 1788, 1485, 1363, 1201, 1103. CI-MS: 211(42, [M+1]⁺), 194(7),

193(57), 189(4), 183(9), 175(8), 171(19), 167(7), 166(27), 152(25). HR-MS: 211.1326 ($C_{12}H_{19}O_3$)⁺, [M+1]⁺; calc. 211.1328.

Trans-8: ¹H-NMR (500 MHz): δ = 5.97-5.83(*m*, 2H, 2 CH=CH₂); 5.27-5.25(*m*, 5H, H-C(2), 2 CH=CH₂); 4.45-4.44(*dd*, J=3.35, 1.6, 1H, H-C(5)); 3.31-3.25(*m*, 1H, CH(CH=CH₂)₂); 0.94(*s*, 9H, *t*-Bu). ¹³C-NMR (126.76 MHz): 172(*s*); 135.4(*s*); 132.4(*s*); 119.2 (*s*); 118.1(*s*); 111.4(*s*); 78.1(*s*); 50.3(*s*); 23.1(*s*).

2-tert-butyl-5-(2-propenyl)-5(1-vinyl-2-propenyl)-1,3-dioxolan-4-one (9): To a solution of LDA (4.2 ml, 4.2 mmol) at -78^oC. a solution of *trans-8* (740 mg, 3.52 mmol) in THF (2.0 ml) was added slowly and stirred for 5 min. A solution of propargyl bromide (2.096 g, 17.6 mmol) in THF (2.0 ml) was added and the solution was allowed to warm up to r.t. After about 2 hrs, saturated solution of NH₄Cl was added and the solution was extracted with Et₂O (3 x 20 ml). combined organic phases was washed with brine and dried over MgSO₄. After evaporation of the solvent the crude was purified by FC (hexane/EtOAc, 20:1), **9** afforded as pale yellow oil and as single isomer, 560.00 mg, 65 %. IR (Film): 3620; 3296; 3084; 2976; 2876; 2360; 1797; 1485; 1410; 1195. ¹H-NMR (500 MHz): δ = 5.92-5.79(*m*, 2H, 2 CH=CH₂); 5.9 (*s*, 1H, HC-*t*-Bu); 5.28-5.12(*m*, 4H, 2CH=C_{HH}); 3.2(*m*, 1H, CH(CH=CH₂)₂); 2.75-2.7(*dd*, 1H, J=17.13, 2.67, HHC-CCH); 2.69-2.59 (*dd*, 1H, J=17.63, 2.67, HHC-CCH); 2.09 (*t*, 1H, J=2.74 CH₂CCH); 1.0 (*s*, 9H, *t*-Bu). ¹³C-NMR (125.7 MHz): 173.06(*s*), 134.9(*s*), 133.9(*s*), 120.15(*s*), 119.2(*s*), 109.83(*s*), 83.7(*s*), 78.3(*s*), 72.3(*s*), 53.7(*s*), 34.9(*s*), 24.7(*s*), 24.27(*s*). CI-MS: 249(8, [M+1]⁺), 209(5), 202(6), 190 (7), 180 (9), 162 (19), 152 (7), 137 (13), 136 (100), 134 (22), 118 (8), 116 (6), 108 (23), 106 (17), 94 (19), 80 (27), 66 (44), 56 (13). Anal. calc. for C₁₅H₂₀O₃(248.322): C 72.55, H 8.12: found: C 72.63, H 8.00.

7-[2-tert-butyl-6-vinyl-1,3'-dioxolan-4noyl]-bicyclo [3.3.0] oct-1-en-3-one (10a): To a solution of **9** (120 mg, 0.48 mmol) in Et₂O (2.0 ml), dicobaltoctacarbonyl (198 mg, 0.58 mmol) was added and stirred at room temperature. After completion of the complex (about 2hrs), Et₂O was evaporated and pure alkyne-cobalt complex (220 mg, 77 %) was obtained after FC (hexane: EtOAc, 20:1). To this cobalt complex in CH₂Cl₂ (10 ml), NMO.H₂O (654 mg, 4.8 mmol) was added and stirred for 5 hrs at r.t. The solution was dried with MgSO₄ and followed by filtration, and the crude product obtained was purified using FC (hexane: EtOAc. 2:1) to afford mixture of products, **10 a** and **10 b** (76 % *ds*, GC). The two diastereomers in the mixture was separated by preparative HPLC. Major (**10 a**); ¹H-NMR (360 MHz); δ = 6.0 (*m*, 1H, HC=CCH₂); 5.9-5.8(*m*, 1H, HC=CH₂); 5.29-5.23(*m*, 2H, CH=C_{HH}); 5.1(*s*, 1H, HC-*t*-Bu); 3.4(*m*,

1H, CH-HC-CH₂); 3.2(*d*, 1H, J=18.31, HHC-C=CH); 2.9(*d*, 1H, J= 18.31, HHC-C=CH); 2.6 (*dd*, J= 18.31, 6.72, HHC-CO); 2.5 (*dd*, 1H, J= 12.51, 8.24, HC-HC=CH₂); 2.1 (*dd*, 1H, J= 18.3, 3.05, HHC-CO) 1.0 (s, 9H, *t*-Bu). ¹³C-NMR (125,7 MHz): 208.8(s); 181.5 (s); 174.0(s); 133.2 (s); 126.9 (s); 121.1 (s); 106.9 (s); 87.8 (s); 66.1 (s); 57.1 (s), 48.5 (s), 34.7 (s), 32.1(s); 25.9 (s). IR (KBr): 2949; 2948; 2897; 2348; 2344; 2281; 1776; 1685; 1641; 1640; 1529; 1210; 1111; 1110; 962; 970. CI-MS: 278 (21 [M+1]⁺); 277 (91); 259 (9); 241 (3); 230 (6); 219 (20); 204(3); 191 (9); 190 (100); 189 (16); 188 (4); 172 (3); 162 (55); 161 (7); 144 (9); 86 (6). Anal calc. for C₁₆H₂₀O₄ (276.33) C 69.55, H 7.30: found C 69.65, H 7.33.