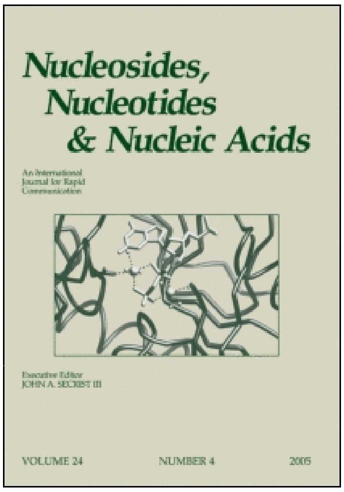

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Synthesis of Carbocyclic 1-[4-(Hydroxymethyl)cyclopent-2-enyl]-1,2,4-triazole-3-carboxamide and Its Derivatives

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ABSTRACT

The synthesis of carbocyclic 1-[4-(hydroxymethyl)cyclopent-2-enyl]-1,2,4-triazole-3-carboxamide (**6a**) and its derivatives was achieved from triol **10** in excellent overall yield. This route involves a Pd(0)-catalyzed coupling reaction as a key step.

Key Words: Carbocyclic nucleoside; Pd(0)-catalyzed; Coupling reaction; Carbocyclic ribavirin analogues.

INTRODUCTION

Carbocyclic analogues of normal purine or pyrimidine nucleosides have received much attention for potential antiviral and antitumor activity.[1] Carbocyclic 2′,3′-didehydro-2′,3′-dideoxyguanosine (carbovir, **1a**)[a] was reported to be an in vitro selective inhibitor of HIV-1 and exhibited greater selectivity than other agents. The analogue of (−)-carbovir, abacavir (**1b**), which has higher oral bioavail-

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[a] For some carbovir syntheses including the syntheses via the Pd(0)-catalyzed coupling reaction of purine base and allylic substrate, see Ref.[2].

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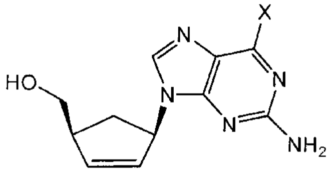
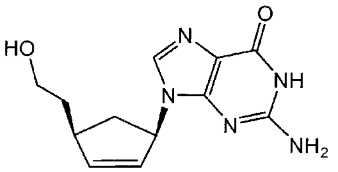
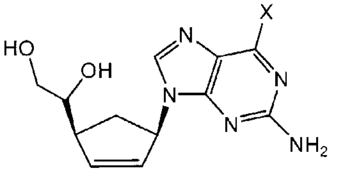


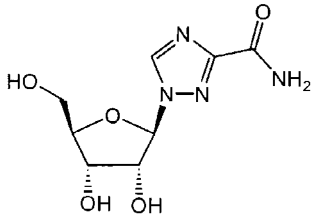
X = OH (Carbovir, **1a**)
X = HN–◁ (Abacavir, **1b**)



5'-Homocarbovir, **2**



X = OH (**3**)
X = HN–◁ (**4**)

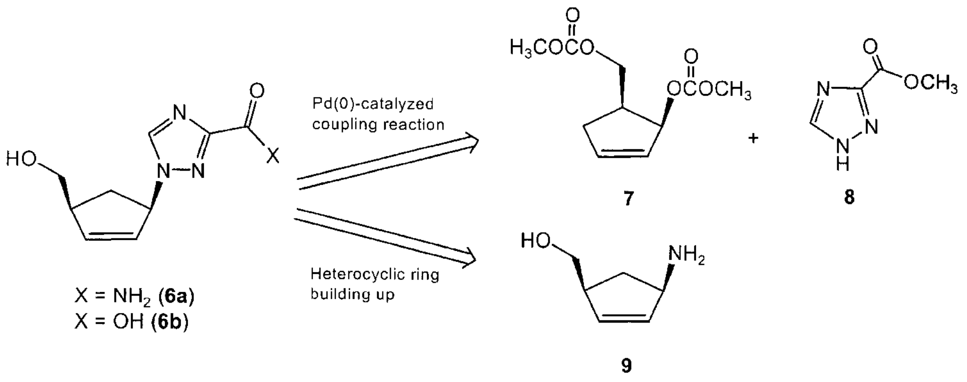


Ribavirin, **5**

ability than carbovir and an improved toxicological profile in vivo,[3] is currently commercialized for the treatment of HIV infection. Because of the important biological activity of these carbocyclic nucleosides, the synthesis of (−)-carbovir analogues has been focused and reported by several research groups.[4] Recently, we synthesized an analogue of carbovir, 5′-homocarbovir (**2**)[4a–4f] and *cis*-9-[4-(1,2-dihydroxyethyl)-cyclopent-2-enyl]guanine (**3**) and *cis*-2-amino-6-cyclopropyl amino-9-[4-(1,2-dihydroxyethyl)-cyclopent-2-enyl]purine (**4**)[4a]. However, antiviral screening revealed that neither compound exhibited anti-HSV or anti-HIV activity. Since the 5′-structural modification of carbovir (**1a**) or abacavir (**1b**) did not afford any biological activities, we decided to modify the nucleoside base of carbocyclic nucleosides.

Ribavirin (**5**) is known as a broad-spectrum antival agent, thus the structural modification of ribavirin (**5**) has been tried by several research groups.[5] In order to search for more potent anti-HIV agents we have chosen the structural modification of nucleoside base to a 1,2,4-triazole-3-carboxamide moiety as is present in ribavirin (**5**).

In this paper, we report a synthetic trial for the carbocyclic nucleosides **6** from triol **10**. Strategically, two general synthetic approaches for 2′,3′-didehydroxycarbocyclic ribavirin (**6a**) can be considered. One is the coupling of the intact heterocyclic base **8** to cyclopentenyl derivative and the other is the construction of the heterocyclic base from the amino alcohol **9**. Since we and other research groups demonstrated efficient preparation methods for *cis*-4-amino-2-cyclopentene-1-methanol (**9**),[3a,6] the synthesis of desired carbocyclic ribavirin analogues **6** can be achieved by the construction of the heterocyclic base from the amino alcohol **9** through a semi-formal synthesis via Saksena's protocol.[5a] However, this protocol has too lengthy steps. Pd(0)-catalyzed coupling reaction of heterocyclic base **8** to cyclopentenyl derivative



7 seems to give a short synthetic route for 2′,3′-didehydroxycarbocyclic ribavirin (**6a**). Thus, we were concentrating this synthetic approach.

RESULTS AND DISCUSSION

Triol **10** was easily prepared from cyclopentadiene and *syn*-diol **11** was prepared from triol **10** by a known procedure.[2j,4a,6] Cleavage of the vicinal diol moiety of triol **10** with sodium periodate followed by sodium borohydride reduction gave a diol **11**. Treatment of diol **11** with methyl chloroformate and 4-dimethylaminopyridine (DMAP) in pyridine afforded the dicarbonate **7** (Sch. 1).

The dicarbonate **7** was then subjected to the Pd(0)-catalyzed coupling reaction with methyl 1,2,4-triazole-3-carboxylate. However, surprisingly, the attempted coupling reaction of the dicarbonate **7** gave undesired product **12** (Sch. 2). The structure of the coupling product **12** was confirmed by X-ray crystallography (Fig. 1).[b] Among the nitrogen atoms in methyl 1,2,4-triazole-3-carboxylate, the coupling occurred at the more hindered N2.[5a][c] Ammonolysis of compound **12** with methanolic ammonia afforded an isomeric carbocyclic ribavirin derivative **13a**.

Hydrolysis of compound **12** with aqueous sodium hydroxide gave a compound **13b** in good yield (Sch. 2). The antiviral screening of carbocyclic nucleosides **13a** and **13b** has been evaluated for cytotoxicity against Vero (african green monkey kidney cell) and MT-4 (HTLV-1-infected human T lymphocyte) and for antiviral activity with herpes simplex virus (HSV) and human immunodefficiency virus (HIV). Antiviral screening showed that compounds **13a** and **13b** did not exhibit any anti-HSV and anti-HIV activity.

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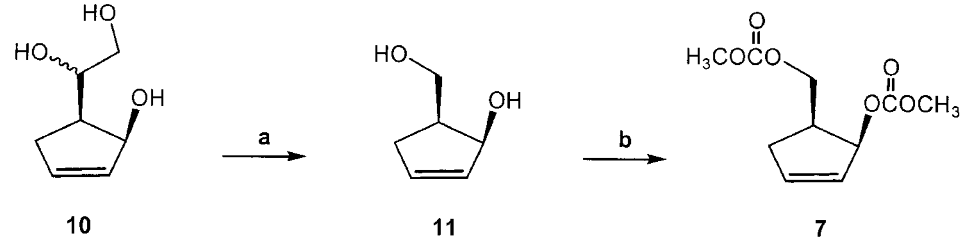
[b] X-Ray crystallographic data for compound. 12 have been submitted for deposition at the Cambridge Crystallographic Data Center (CCDC 196934).

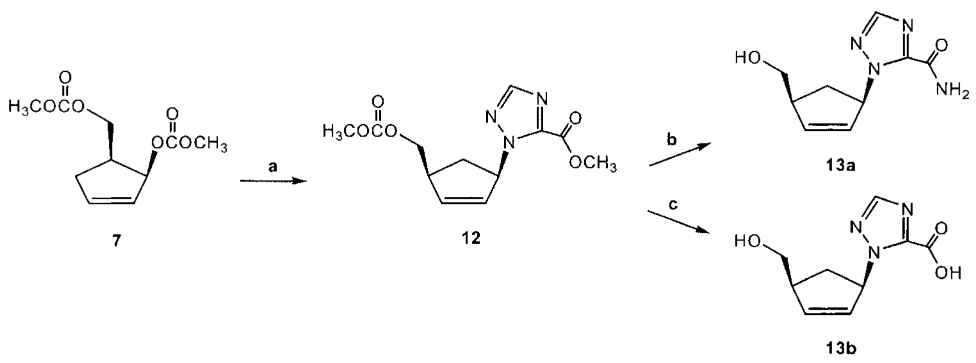
[c] Saksena et al. reported that the alkylation of the more hindered nitrogen of ethyl 1,2,4-triazole-3-carboxylate was also observed at the nucleophilic displacement of the triflate compound; see, reference 5a.



Scheme 1. **a.** i) $NaIO_4$, diethyl ether/H_2O, 2 h. ii) ethylene glycol, 1 h. iii) $NaBH_4$, 2 h, 70%. **b**. methyl chloroformate, DMAP (cat.), pyridine, 0°C, 30 min, 93%.

Since the direct Pd(0)-catalyzed coupling reaction with methyl 1,2,4-triazole-3-carboxylate (**8**) gave undesired product **12**, the coupling partner of dicarbonate **7** was changed to ethyl oxalamidrazonate. This compound was easily prepared by the known procedure.[7] It is presumed that the Pd(0)-catalyzed coupling reaction of dicarbonate **7** occurs at the terminal amino group of hydrazine moiety of ethyl oxalamidrazonate since this site would be the most nucleophilic toward π-allyl palladium complex. Upon the Pd(0)-catalyzed coupling reaction with ethyl oxalamidrazonate, the coupling adduct **14** was obtained in 93% yield. The construction of the triazole ring was achieved by the reaction of compound **14** with trimethyl orthoformate. The desired compounds **6a**, **6b**, **16**, and **17** were obtained by the reaction of compound **15** with ammonia, sodium hydroxide, cyclopropylamine, and ethanolic HCl, respectively (Sch. 3).

In summary, the short synthesis of 2′,3′-didehydroxycarbocyclic ribavirin analogues, **6a**, **6b**, **16**, and **17** was achieved from triol **10** in 52, 52, 48 and 51% overall yields, respectively. The antiviral screening of carbocyclic nucleosides, **6a**, **6b**, **16**, and **17** is currently under investigation. We hope this synthetic protocol can be a useful method for the synthesis of other carbocyclic nucleoside analogues.



Scheme 2. **a**. i) $Pd(OAc)_2$, $(i\text{-}PrO)_3P$, THF, rt ii) n-BuLi, rt iii) **7** in THF iv) 1,2,4-triazole-3-carboxylic acid methyl ester (**8**) in DMSO, 12 h, 82% **b**. 2.0 M NH_3 in methanol, rt, 1 d, 83% **c**. 0.25 N NaOH(aq), reflux, 1 h, 82%.

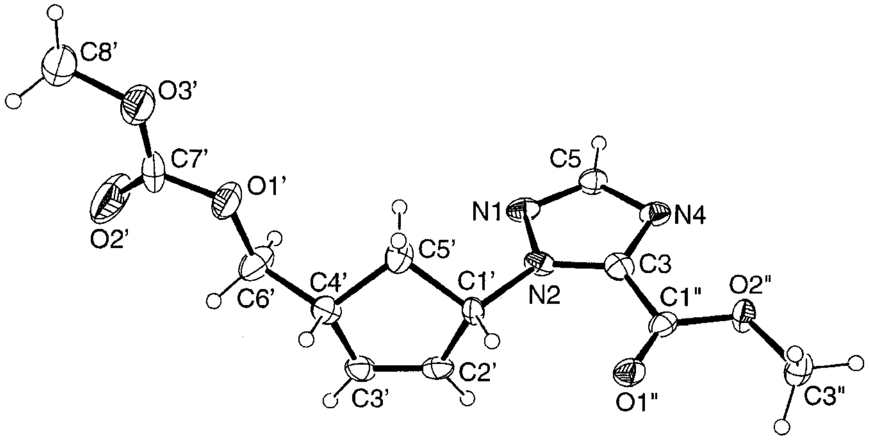
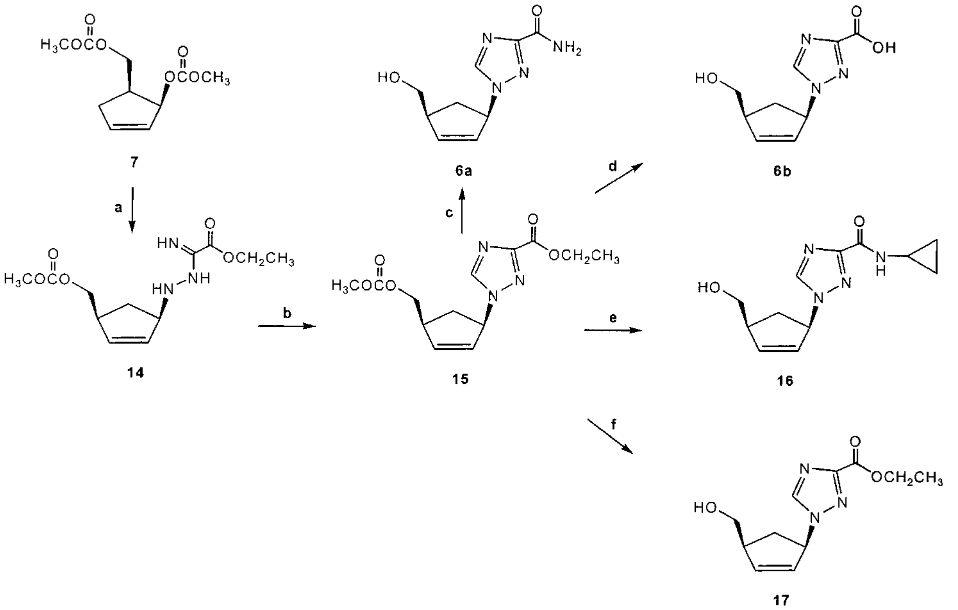


Figure 1. The structure of the compound **12** by X-ray crystallography.



Scheme 3. **a**. i) $Pd(OAc)_2$, $(i\text{-}PrO)_3P$, THF, rt ii) *n*-BuLi, rt iii) **7** in THF iv) ethyl oxalamidrazonate in THF, 2 h, 93% **b**. trimethyl orthoformate (excess), reflux, 30 min, 92% **c**. 2.0 *M* NH_3 in methanol, rt, 1 d, 94% **d**. 0.1 *N* aq. NaOH, reflux, 1h, 93% **e**. cyclopropylamine (excess), reflux, 1d, 87% **f**. 5.0% ethanolic HCl, rt, 4 h, 91%.

EXPERIMENTAL

Proton (^1H) NMR spectra were obtained using a Varian Mercury 300 spectrometer (300 MHz) instrument operating in Fourier transform mode. Carbon-13 (^{13}C) NMR spectra were recorded using a Varian Mercury 300 spectrometer (75.5 MHz) instrument. Infrared spectra were recorded on Bio-Rad FTS 6000 FT-IR spectrometer. Uncorrected melting points were determined with a Gallenkamp melting point apparatus. Analytical thin layer chromatography (TLC) was conducted on E. Merck 60 F254 aluminum backed silica gel plates (0.2 mm) with a fluorescent indicator. Developed plates were visualized under UV light, with iodine staining, or by dipping in 2.0% phosphomolybdic acid solution and then heating. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh) under positive pressure of air according to the procedure of Still.[8] Reagents and solvents were of reagent grade, and solvents were purified by the known procedure before use.[9]

***cis*-5-Hydroxymethyl-cyclopent-2-en-1-ol (11).** Diol **11** was prepared from triol **10** by a known procedure:[6a] IR (thin film) 3423, 3058, 2930, 1615, 1441, 1350, 1155, 1019, 951, 891, 723 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.98 (m, 1H), 5.82 (m, 1H), 4.89 (m, 1H), 3.78 (m, 2H), 3.30 (br s, 1H), 3.06 (br s, 1H), 2.43 (m, 1H), 2.32 (m, 1H), 2.16 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 135.01, 132.30, 77.69, 62.69, 42.59, 33.65.

***cis*-Methyl 5-(methoxycarbonyloxymethyl)-cyclopent-2-enyl-1-carbonate (7).** To a solution of diol **11** (2.00 g, 17.5 mmol) in anhydrous $CHCl_3$ (20 mL) was added pyridine (10 mL mmol) and DMAP (0.170 g, 1.38 mmol) at 0°C. Then, methyl chloroformate (20.3 mL, 263.1 mmol) in pyridine (10 mL) was slowly added by dropping funnel at 0°C. After being stirred for 30 min, the reaction mixture was diluted with $CHCl_3$ (30 mL) and washed with brine solution (30 mL × 3). The aqueous phase was extracted with $CHCl_3$ (50 mL). The organic phase was collected, dried with anhydrous $MgSO_4$, and concentrated by rotary-evaporation. The residue was purified by flash column chromatography (diethyl ether:hexane = 2:7, v/v) to give a colorless oil **7** ($R_f = 0.24$; 3.73 g, 93%): IR (thin film) 2958, 2916, 2855, 1742, 1442, 1252, 945, 788 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.14 (m, 1H), 5.91 (m, 1H), 5.62 (dd, $J = 4.5$, 1.8 Hz, 1H), 4.35 (m, 1H), 4.22 (m, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.75 (dd, $J = 14.7$, 7.2 Hz, 1H), 2.50 (m, 1H), 2.30 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 155.52, 155.20, 137.67, 128.84, 82.01, 66.81, 54.84, 54.74, 39.92, 34.65.

***cis*-Methyl 2-[4-(hydroxymethyl)-cyclopent-2-enyl]-1,2,4-triazole-3-carboxylate (12).** Triisopropyl phosphite (0.63 mL, 2.54 mmol) was added at ambient temperature to a solution of $Pd(OAc)_2$ (0.14 g, 0.83 mmol) in anhydrous THF (15.0 mL) under argon. After being stirred for 15 min, *n*-BuLi (1.6 *N* in hexane, 1.54 mL, 2.54 mmol) was added at ambient temperature. The resulting mixture was stirred for 15 min to obtain tetrakis (triisopropylphosphite)palladium (0) catalyst. The in situ prepared Pd(0) catalyst was added to a solution of methyl 1,2,4-triazole-3-carboxylate (1.78 g, 14.01 mmol) in anhydrous DMSO (25.0 mL) via cannula at ambient temperature. Then, a solution of dicarbonate **7** (2.92 g, 12.73 mmol) in anhydrous THF (10 mL) was added to the reaction mixture. After being stirred for 12 h, the reaction mixture was diluted with ethyl acetate (30 mL) and washed with brine solution (20 mL × 3). The aqueous phase was extracted with ethyl acetate (40 mL × 2). The organic phase was collected, dried with anhydrous $MgSO_4$, and concentrated by rotary-evaporation. The residue was purified by flash column chromatography (ethyl acetate:hexane = 1:1, v/v) to give a white solid **12** ($R_f = 0.23$; 3.27 g, 82%):

m.p., 100–102°C; IR (KBr pellet) 1750, 1724, 1275, 1242, 1090, 791, 770, 589 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.12 (s, 1H), 6.20 (m, 1H), 6.01 (m, 1H), 5.87 (m, 1H), 4.13 (m, 2H), 3.90 (s, 3H), 3.68 (s, 3H), 3.08 (m, 1H), 2.64 (m, 1H), 1.80 (m, 1H); ^{13}C NMR (DMSO-d$_6$) δ 157.99, 154.92, 150.38, 143.61, 134.96, 131.26, 69.85, 65.05, 54.58, 52.83, 43.74, 33.32.

***cis*-2-[4-(Hydroxymethyl)-cyclopent-2-enyl]-1,2,4-triazole-3-carboxamide (13a).** The coupling adduct **12** (0.1 g, 0.36 mmol) was added to 2.0 *M* methanolic NH_3 (10 mL). The mixture was stirred at ambient temperature for 1 d. Silica gel (~2.0 g) was added to this solution and then the resulting suspension was dried under the reduced pressure. By the pre-loaded silica gel column chromatography (chloroform:methanol = 15:1, v/v), a white solid **13a** ($R_f = 0.25$; 0.06 g, 83%) was obtained: m.p., 116–118°C ; IR (KBr pellet) 3318, 3206, 1702, 1653, 1506, 1279, 579 cm^{-1}; ^{1}H NMR (Acetone-d_6) δ 7.89 (s, 1H), 7.68 (br s, 1H), 7.20 (br s, 1H), 6.59 (m, 1H), 6.06 (dd, $J = 5.4$, 3.9 Hz, 1H), 5.80 (dd, $J = 5.4$, 3.9 Hz, 1H), 3.83 (br s, 1H), 3.61 (m, 2H), 2.95 (m, 1H), δ2.67 (m, 1H), 1.85 (m, 1H); ^{13}C NMR (Acetone-d_6) δ 159.77, 150.16, 137.24, 131.95, 131.13, 66.18, 48.91, 41.33, 34.59.

***cis*-2-[4-(Hydroxymethyl)-cyclopent-2-enyl]-1,2,4-triazole-3-carboxylic acid (13b).** The coupling adduct **12** (0.15 g, 0.533 mmol) was added to 0.25 *N* aqueous NaOH (10 mL). The mixture was stirred at reflux temperature for 1 h. Then, the reaction mixture was neutralized to *p*H 7–8 with diluted HCl. After removal of water by rotary-evaporation, the residue was diluted with methanol (20 mL). Silica gel (~2.0 g) was added to this solution and then the resulting suspension was dried under the reduced pressure. By the pre-loaded silica gel column chromatography (chloroform:methanol = 1:1, v/v), a white solid **13b** ($R_f = 0.30$; 0.09 g, 82%) was obtained: m.p., 119°C (decomp.); IR (KBr pellet) 3456, 1635, 1506, 1403, 1289, 1085, 1030, 996, 831, 669 cm^{-1}; ^{1}H NMR (D_2O) δ 7.94 (s, 1H), 6.25 (m, 1H), 6.11 (m, 1H), 5.87 (m, 1H), 3.62 (m, 2H), 3.01 (m, 1H), 2.74 (m, 1H), 1.63 (m, 1H); ^{13}C NMR (D_2O) δ 158.59, 145.30, 144.50, 142.03, 125.19, 107.90, 60.39, 42.15, 29.60.

Ethyl oxalamidrazonate. Ethyl oxalamidrazonate was prepared from ethyl oxamate by a known procedure:[7] m.p., 87–88°C; IR (KBr pellet) 3364, 3116, 2925, 2873, 1734, 1718, 1457, 1218, 1029, 846, 799, 678, 663 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.67 (br s, 2H), 5.34 (br s, 2H), 4.13 (q, $J = 7.2$ Hz, 2H), 1.21 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 163.06, 136.06, 61.17, 14.78.

***cis*-Ethyl *N*-[4-(methoxycarbonyloxymethyl)-cyclopent-2-enyl]-oxalamidrazonate (14).** Triisopropyl phosphite (0.17 mL, 0.69 mmol) was added at ambient temperature to a solution of $Pd(OAc)_2$ (0.039 g, 0.17 mmol) in anhydrous THF (4.0 mL) under argon. After being stirred for 15 min, *n*-BuLi (1.6 *N* in hexane, 0.43 mL, 0.69 mmol) was added at ambient temperature. The resulting mixture was stirred for 15 min to obtain tetrakis (triisopropylphosphite)palladium (0) catalyst. The in situ prepared Pd(0) catalyst was added to a solution of ethyl oxalamidrazonate (0.45 g, 3.46 mmol) in anhydrous THF (6.0 mL) via cannula at ambient temperature. Then, a solution of dicarbonate **7** (0.79 g, 3.46 mmol) in anhydrous THF (5.0 mL) was added to the reaction mixture. After being stirred for 2 h, the reaction mixture was diluted with chloroform (15 mL) and washed with brine solution (20 mL × 3). The aqueous phase was extracted with chloroform (15 mL × 2). The organic phase was collected, dried with anhydrous $MgSO_4$ and concentrated by rotary-evaporation. The residue was purified by flash column chromatography (ethyl acetate:hexane = 1:1, v/v) to give a pale yellow gummy solid ($R_f = 0.23$; 0.92 g, 93%): IR (thin film) 3446, 3325, 3189, 3153, 2983, 2917, 2852, 1718, 1700, 1653, 1559, 1234, 1027, 915, 850, 784 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.94 (dd, $J = 4.8$, 3.6 Hz, 1H), 5.80 (dd, $J = 3.6$, 2.1 Hz, 1H), 4.54 (m, 1H), 4.42 (br s, 2H), 4.34 (q, $J = 7.2$ Hz, 2H), 4.21 (dd, $J = 10.7$, 4.8 Hz, 1H), 4.08 (dd, $J = 10.5$, 5.1 Hz, 1H), 3.77 (s, 3H), 2.97 (br s, 1H), 2.49 (m, 1H), 1.49 (m, 1H), 1.35 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.27, 155.77, 136.88, 134.47, 133.82, 70.49, 66.18, 62.33, 55.03, 44.16, 33.81, 14.44.

***cis*-Ethyl 1-[4-(methoxycarbonyloxymethyl)-cyclopent-2-enyl]-1,2,4-triazole-3-carboxylate (15).** The coupling adduct **14** (0.70 g, 2.44 mmol) was added to anhydrous toluene (5 mL). Then, a solution of trimethyl orthoformate (1.07 mL, 9.78 mmol) in anhydrous toluene (10.0 mL) was added to the reaction mixture. The mixture was stirred at reflux temperature. After being stirred for 30 min, the reaction mixture was diluted with chloroform (15 mL) and washed with brine solution (20 mL). The aqueous phase was extracted with chloroform (15 mL × 3). The organic phase was collected, dried with anhydrous $MgSO_4$ and concentrated by rotary-evaporation. The residue was purified by flash column chromatography (ethyl acetate:hexane = 2:1, v/v) to give a white solid ($R_f = 0.23$; 0.66 g, 92%): m.p.,96–97°C; IR (thin film) 3119, 1750, 1724, 1503, 1462, 1275, 1242, 1090, 771, 612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25 (s, 1H), 6.19 (m, 1H), 5.98 (m, 1H), 5.61 (m, 1H), 4.49 (q, $J = 6.9$ Hz, 2H), 4.26 (dd, $J = 11.0$, 5.1 Hz, 1H), 4.15 (dd, $J = 10.8$, 5.1 Hz, 1H), 3.78 (s, 3H), 3.19 (m, 1H), 2.88 (m, 1H), 1.85 (m, 1H), 1.44 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159.69, 155.43, 154.54, 142.98, 138.29, 129.26, 69.19, 66.16, 61.70, 54.79, 44.38, 34.32, 14.13.

***cis*-1-[4-(Hydroxymethyl)-cyclopent-2-enyl]-1,2,4-triazole-3-carboxamide (6a).** The compound **15** (0.10 g, 0.34 mmol) was added to 2.0 *M* methanolic NH_3 (10 mL) at −15°C. The mixture was stirred at ambient temperature for 1 d. Silica gel (~2.0 g) was added to this solution and then the resulting suspension was dried under the reduced pressure. By the pre-loaded silica gel column chromatography (chloroform:methanol = 9:1, v/v), a white solid ($R_f = 0.25$; 0.066 g, 94%) was obtained: m.p., 122–123°C; IR (KBr pellet) 3330, 3313, 3226, 1712, 1643, 1536, 1267, 568 cm^{-1}; ^1H NMR (Methanol-d_4) δ 8.50 (s, 1H), 6.20 (m, 1H), 5.94 (m, 1H), 5.61 (m, 1H), 3.61 (d, $J = 5.4$ Hz, 2H), 3.00 (m, 1H), 2.74 (m, 1H), 1.86 (m, 1H); ^{13}C NMR (Methanol-d_4) δ 163.70, 157.86, 145.28, 140.24, 130.28, 67.71, 65.78, 49.31, 35.31.

***cis*-1-[4-(Hydroxymethyl)-cyclopent-2-enyl]-1,2,4-triazole-3-carboxylic acid (6b).** The compound **15** (0.10 g, 0.34 mmol) was added to 0.25 *N* aqueous NaOH (10 mL). The mixture was stirred at reflux temperature for 1 h. Then, the reaction mixture was neutralized to *p*H 7–8 with diluted HCl. After removal of water by rotary-evaporation, the residue was diluted with methanol (20 mL). Silica gel (~2.0 g) was added to this solution and then the resulting suspension was dried under the reduced pressure. By the pre-loaded silica gel column chromatography (chloroform:methanol = 2:3, v/v), a white solid ($R_f = 0.30$; 0.65 g, 93%) was obtained: m.p., 193°C (decomp.); IR (KBr pellet) 3466, 1637, 1422, 1298, 1076, 976, 834, 668 cm^{-1}; ^1H NMR (D_2O) δ 8.40 (s, 1H), 6.21 (m, 1H), 5.98 (m, 1H), 5.58 (m, 1H), 3.62 (d, $J = 5.7$ Hz, 2H), 3.03 (m, 1H), 2.75 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (D_2O) δ 166.54, 158.91, 143.90, 139.01, 129.05, 66.05, 64.35, 47.13, 34.07.

***cis*-1-[4-(Hydroxymethyl)-cyclopent-2-enyl]-1,2,4-triazole-3-*N*-cyclopropyl-carboxamide (16).** Cyclopropylamine (0.22 mL, 3.0 mmol) was added to a solution of the compound **15** (0.10 g, 0.34 mmol) in ethanol (5.0 mL) and then the reaction mixture was stirred at 100°C in autoclave. After being stirred for 12 h, the more cyclopropylamine (0.11 mL, 1.5 mmol) was added to reaction mixture and stirred for 12 h. The reaction mixture was concentrated by rotary-evaporation. The crude reaction mixture was washed with chloroform (3 mL × 3) and was diluted with methanol (30 mL). Silica gel (~2.0 g) was added to this solution and then the

Table 1. Crystal data and structure refinement for compound **12**.

Identification code	d:_577_1_57mo
Empirical formula	C12 H15 N3 O5
Formula weight	281.27
Temperature	173(1) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P\ 2_1$
Unit cell dimensions	a = 4.5653(12) Å α = 90°. b = 53.386(14) Å β = 101.451(5)°. c = 5.3578(14) Å γ = 90°.
Volume	1279.8(6) $Å^3$
Z	4
Density (calculated)	1.460 mg/m^3
Absorption coefficient	0.115 mm^{-1}
F(000)	592
Crystal size	0.25 × 0.20 × 0.04 mm^3
Theta range for data collection	0.76 to 28.33°.
Index ranges	$-6 \Leftarrow h \Leftarrow 6$, $-69 \Leftarrow k \Leftarrow 69$, $-7 \Leftarrow l \Leftarrow 7$
Reflections collected	25907
Independent reflections	6120 [R(int) = 0.0927]
Completeness to theta = 28.33°	97.7%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9954 and 0.9718
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6120/1/365
Goodness-of-fit on F^2	1.088
Final R indices [I > 2sigma(I)]	R1 = 0.0823, wR2 = 0.2003
R indices (all data)	R1 = 0.1261, wR2 = 0.2192
Absolute structure parameter	2(2)
Largest diff. peak and hole	0.394 and −0.368 e.$Å^{-3}$

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for compound **12**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1A)	6914(10)	3659(1)	3980(8)	24(1)
N(2A)	8735(9)	3681(1)	2309(8)	20(1)
C(3A)	9234(11)	3924(1)	1951(10)	22(1)
N(4A)	7851(10)	4068(1)	3402(8)	22(1)
C(5A)	6505(12)	3895(1)	4617(10)	22(1)
C(1′A)	9698(11)	3454(1)	1140(10)	19(1)
C(2′A)	7187(13)	3327(1)	−658(10)	23(1)
C(3′A)	7254(13)	3083(1)	−391(11)	26(1)
C(4′A)	9719(12)	3001(1)	1688(10)	23(1)
C(5′A)	10746(12)	3244(1)	3092(11)	26(1)
C(6′A)	8649(14)	2798(1)	3322(12)	34(1)
C(7′A)	10838(15)	2522(1)	6542(13)	35(1)
C(8′A)	12995(19)	2288(1)	10108(14)	54(2)
O(1′A)	11121(10)	2738(1)	5407(8)	35(1)
O(2′A)	8978(13)	2369(1)	5868(11)	70(2)
O(3′A)	12973(10)	2510(1)	8622(9)	42(1)
C(1″A)	11066(12)	4022(1)	140(10)	21(1)
O(1″A)	12421(9)	3891(1)	−1091(7)	25(1)
O(2″A)	11013(8)	4269(1)	117(7)	23(1)
C(3″A)	12746(12)	4390(1)	−1550(11)	25(1)
N(1B)	−2150(10)	439(1)	11590(8)	24(1)
N(2B)	−322(9)	420(1)	9837(8)	19(1)
C(3B)	237(11)	175(1)	9526(9)	17(1)
N(4B)	−1125(10)	32(1)	10939(8)	20(1)
C(5B)	−2508(12)	198(1)	12148(10)	25(1)
C(1′B)	494(12)	653(1)	8680(10)	26(1)
C(2′B)	−2076(12)	768(1)	6913(10)	23(1)
C(3′B)	−2139(14)	1014(1)	7304(11)	29(1)
C(4′B)	373(13)	1104(1)	9366(11)	28(1)
C(5′B)	1688(13)	855(1)	10602(10)	23(1)
C(6′B)	−782(14)	1277(1)	11182(12)	33(1)
C(7′B)	2982(14)	1567(1)	13065(12)	33(1)
C(8′B)	6686(16)	1834(1)	15273(15)	48(2)
O(1′B)	1659(10)	1347(1)	13269(8)	38(1)
O(2′B)	2320(12)	1712(1)	11346(10)	52(1)
O(3′B)	5084(10)	1594(1)	15160(8)	39(1)
C(1″B)	2053(11)	77(1)	7744(9)	16(1)
O(1″B)	3379(8)	208(1)	6480(7)	21(1)
O(2″B)	1977(9)	−171(1)	7623(7)	24(1)
C(3″B)	3701(13)	−284(1)	5994(11)	28(1)

Table 3. Bond lengths [Å] and angles [°] for compound **12**.

N(1A)-C(5A)	1.327(7)	C(3A)-N(4A)-C(5A)	101.5(4)
N(1A)-N(2A)	1.343(6)	N(1A)-C(5A)-N(4A)	115.2(5)
N(2A)-C(3A)	1.337(7)	N(2A)-C(1′A)-C(2′A)	112.9(4)
N(2A)-C(1′A)	1.472(6)	N(2A)-C(1′A)-C(5′A)	112.9(4)
C(3A)-N(4A)	1.338(7)	C(2′A)-C(1′A)-C(5′A)	101.6(4)
C(3A)-C(1″A)	1.495(7)	C(3′A)-C(2′A)-C(1′A)	112.3(5)
N(4A)-C(5A)	1.347(7)	C(2′A)-C(3′A)-C(4′A)	111.9(5)
C(1′A)-C(2′A)	1.504(8)	C(3′A)-C(4′A)-C(5′A)	103.4(5)
C(1′A)-C(5′A)	1.541(7)	C(3′A)-C(4′A)-C(6′A)	111.0(4)
C(2′A)-C(3′A)	1.308(8)	C(5′A)-C(4′A)-C(6′A)	114.9(5)
C(3′A)-C(4′A)	1.484(8)	C(4′A)-C(5′A)-C(1′A)	105.0(4)
C(4′A)-C(5′A)	1.526(7)	O(1′A)-C(6′A)-C(4′A)	107.9(4)
C(4′A)-C(6′A)	1.534(7)	O(2′A)-C(7′A)-O(1′A)	126.3(6)
C(6′A)-O(1′A)	1.458(7)	O(2′A)-C(7′A)-O(3′A)	125.8(6)
C(7′A)-O(2′A)	1.183(8)	O(1′A)-C(7′A)-O(3′A)	107.9(5)
C(7′A)-O(1′A)	1.320(7)	C(7′A)-O(1′A)-C(6′A)	114.4(5)
C(7′A)-O(3′A)	1.328(8)	C(7′A)-O(3′A)-C(8′A)	115.6(5)
C(8′A)-O(3′A)	1.427(8)	O(1″A)-C(1″A)-O(2″A)	125.6(5)
C(1″A)-O(1″A)	1.212(6)	O(1″A)-C(1″A)-C(3A)	124.2(5)
C(1″A)-O(2″A)	1.317(6)	O(2″A)-C(1″A)-C(3A)	110.1(4)
O(2″A)-C(3″A)	1.458(6)	C(1″A)-O(2″A)-C(3″A)	116.1(4)
N(1B)-C(5B)	1.334(7)	C(5B)-N(1B)-N(2B)	101.7(4)
N(1B)-N(2B)	1.378(6)	C(3B)-N(2B)-N(1B)	107.9(4)
N(2B)-C(3B)	1.350(6)	C(3B)-N(2B)-C(1′B)	134.3(4)
N(2B)-C(1′B)	1.470(7)	N(1B)-N(2B)-C(1′B)	117.8(4)
C(3B)-N(4B)	1.314(6)	N(4B)-C(3B)-N(2B)	111.6(4)
C(3B)-C(1″B)	1.479(7)	N(4B)-C(3B)-C(1″B)	123.8(4)
N(4B)-C(5B)	1.329(7)	N(2B)-C(3B)-C(1″B)	124.5(4)
C(1′B)-C(2′B)	1.486(8)	C(3B)-N(4B)-C(5B)	102.7(4)
C(1′B)-C(5′B)	1.514(7)	N(4B)-C(5B)-N(1B)	116.1(5)
C(2′B)-C(3′B)	1.327(8)	N(2B)-C(1′B)-C(2′B)	112.6(4)
C(3′B)-C(4′B)	1.505(8)	N(2B)-C(1′B)-C(5′B)	113.7(4)
C(4′B)-C(6′B)	1.510(8)	C(2′B)-C(1′B)-C(5′B)	105.8(4)
C(4′B)-C(5′B)	1.553(7)	C(3′B)-C(2′B)-C(1′B)	110.3(5)
C(6′B)-O(1′B)	1.462(7)	C(2′B)-C(3′B)-C(4′B)	113.3(5)
C(7′B)-O(2′B)	1.197(7)	C(3′B)-C(4′B)-C(6′B)	110.9(5)
C(7′B)-O(3′B)	1.332(7)	C(3′B)-C(4′B)-C(5′B)	102.2(4)
C(7′B)-O(1′B)	1.336(7)	C(6′B)-C(4′B)-C(5′B)	113.8(5)
C(8′B)-O(3′B)	1.471(8)	C(1′B)-C(5′B)-C(4′B)	105.2(4)
C(1″B)-O(1″B)	1.214(6)	O(1′B)-C(6′B)-C(4′B)	109.8(5)
C(1″B)-O(2″B)	1.324(6)	O(2′B)-C(7′B)-O(3′B)	127.5(6)
C(2″B)-C(3″B)	1.420(6)	O(2′B)-C(7′B)-O(1′B)	125.8(6)
C(5A)-N(1A)-N(2A)	103.1(4)	O(3′B)-C(7′B)-O(1′B)	106.7(5)
C(3A)-N(2A)-N(1A)	109.0(4)	C(7′B)-O(1′B)-C(6′B)	116.8(5)
C(3A)-N(2A)-C(1″A)	131.7(4)	C(7′B)-O(3′B)-C(8′B)	113.4(5)
N(1A)-N(2A)-C(1′A)	119.2(4)	O(1″B)-C(1″B)-O(2″B)	123.9(5)
N(2A)-C(3A)-N(4A)	111.1(5)	O(1″B)-C(1″B)-O(3B)	124.2(4)
N(2A)-C(3A)-C(1″A)	124.4(5)	O(2″B)-C(1″B)-C(3B)	111.9(4)
N(4A)-C(3A)-C(1″A)	124.4(5)	C(1″B)-O(2″B)-C(3″B)	116.3(4)

Symmetry transformations used to generate equivalent atoms.

Table 4. Anisotropic displacement parameters ($\text{Å}^2 \times 10^3$) compound **12**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*b^*\ U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1A)	23(2)	34(3)	17(2)	1(2)	9(2)	−2(2)
N(2A)	17(2)	27(2)	18(2)	−5(2)	11(2)	−1(2)
C(3A)	15(3)	25(3)	21(3)	−2(2)	−4(2)	0(2)
N(4A)	21(2)	28(3)	16(2)	1(2)	2(2)	6(2)
C(5A)	21(3)	26(3)	20(3)	0(2)	8(2)	−1(2)
C(1′A)	23(3)	14(2)	23(3)	−1(2)	13(2)	0(2)
C(2′A)	24(3)	31(3)	15(3)	−1(2)	7(2)	5(2)
C(3′A)	31(3)	27(3)	20(3)	−4(2)	8(2)	−12(2)
C(4′A)	23(3)	25(3)	23(3)	−2(2)	8(2)	−6(2)
C(5′A)	24(3)	24(3)	29(3)	4(2)	3(2)	1(2)
C(6′A)	29(3)	38(3)	29(3)	12(3)	−4(3)	−9(3)
C(7′A)	42(3)	15(3)	48(4)	3(2)	11(3)	4(2)
C(8′A)	76(5)	32(4)	46(4)	5(3)	−8(4)	−1(4)
O(1′A)	39(2)	26(2)	35(2)	11(2)	−7(2)	−6(2)
O(2′A)	84(4)	48(3)	63(4)	30(3)	−22(3)	−30(3)
O(3′A)	48(3)	32(2)	42(3)	6(2)	−4(2)	−1(2)
C(1″A)	20(3)	24(3)	17(3)	4(2)	0(2)	−2(2)
O(1″A)	29(2)	28(2)	21(2)	2(2)	12(2)	1(2)
O(2″A)	26(2)	15(2)	32(2)	3(2)	16(2)	1(2)
C(3″A)	24(3)	23(3)	31(3)	5(2)	16(2)	0(2)
N(1B)	21(2)	33(3)	19(2)	−2(2)	5(2)	0(2)
N(2B)	18(2)	17(2)	21(2)	−1(2)	1(2)	3(2)
C(3B)	18(2)	20(3)	12(2)	−2(2)	1(2)	2(2)
N(4B)	24(2)	17(2)	20(2)	−3(2)	7(2)	−8(2)
C(5B)	21(3)	34(3)	18(3)	−1(2)	1(2)	−4(2)
C(1′B)	30(3)	21(3)	27(3)	−1(2)	5(2)	−2(2)
C(2′B)	26(3)	25(3)	16(3)	1(2)	1(2)	2(2)
C(3′B)	39(3)	27(3)	21(3)	6(2)	7(3)	−6(2)
C(4′B)	40(3)	14(3)	29(3)	1(2)	9(3)	−2(2)
C(5′B)	27(3)	15(3)	26(3)	−1(2)	2(2)	0(2)
C(6′B)	38(4)	26(3)	31(3)	−3(2)	−8(3)	2(2)
C(7′B)	37(3)	27(3)	34(3)	2(2)	5(3)	5(3)
C(8′B)	45(4)	44(4)	52(4)	−13(3)	1(3)	−10(3)
O(1′B)	47(3)	24(2)	39(3)	2(2)	0(2)	−5(2)
O(2′B)	60(3)	35(3)	54(3)	13(2)	−8(3)	−6(2)
O(3′B)	43(2)	33(2)	34(2)	1(2)	−7(2)	−7(2)
C(1″B)	12(2)	19(3)	15(3)	−3(2)	−5(2)	−1(2)
O(1″B)	21(2)	21(2)	24(2)	1(2)	10(2)	1(2)
O(2″B)	31(2)	17(2)	29(2)	−1(2)	14(2)	−1(2)
C(3″B)	34(3)	23(3)	27(3)	−1(2)	6(3)	11(2)

resulting suspension was dried under the reduced pressure. By the pre-loaded silica gel column chromatography (chloroform:methanol = 17:1, v/v), a pale yellow gummy solid ($R_f = 0.25$; 0.073 g, 87%) was obtained: IR (thin film) 3405, 3336, 3096, 3008, 2926, 2873, 1684, 1541, 1488, 1256, 1210, 1037, 956, 758, 663 cm^{-1}; ^1H NMR ($CDCl_3$)

δ 8.17 (s, 1H), 6.06 (m, 1H), 5.73 (m, 1H), 5.39 (br s, 1H), 4.09 (br s, 1H), 3.56 (d, $J = 5.1$ Hz, 2H), 2.89 (br s, 1H), 2.74 (m, 1H), 2.60 (m, 1H), 1.76 (m, 1H), 0.73–0.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 160.57, 156.31, 142.80, 139.90, 128.44, 66.26, 64.33, 47.63, 33.97, 22.39, 6.50.

***cis*-Ethyl 1-[4-(Hydroxymethyl)-cyclopent-2-enyl]-1,2,4-triazole-3-carboxylate (17).** The compound **15** (0.10 g, 0.34 mmol) was added to ethanol (8 mL). Then, 5% ethanolic HCl solution (7.0 mL) was added to the reaction mixture. After being stirred at ambient temperature for 4 h, the reaction mixture was concentrated by rotary-evaporation. The residue was purified by the pre-loaded column chromatography (chloroform:methanol = 17:1, v/v) to give a white solid ($R_f = 0.25$; 0.073 g, 91%): m.p., 64–66°C; IR (thin film) 3430, 3112, 2959, 2922, 1734, 1718, 1260, 1217, 1027, 944, 844, 791, 777, 677 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.27 (s, 1H), 6.21 (m, 1H), 5.91 (m, 1H), 5.56 (d, $J = 7.2$ Hz, 1H), 4.46 (q, $J = 7.2$ Hz, 2H), 3.75 (d, $J = 15.3$ Hz, 2H), 3.06 (br s, 1H), 2.79 (m, 1H), 2.40 (br s, 1H), 1.92 (m, 1H), 1.42 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159.99, 154.91, 143.36, 140.16, 129.03, 66.66, 64.91, 62.13, 47.75, 34.38, 14.47.

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