Pergamon

Tetrahedron Letters 42 (2001) 1427–1431

TETRAHEDRON LETTERS

Synthesis of medium-sized rings using the intramolecular Pauson–Khand reaction

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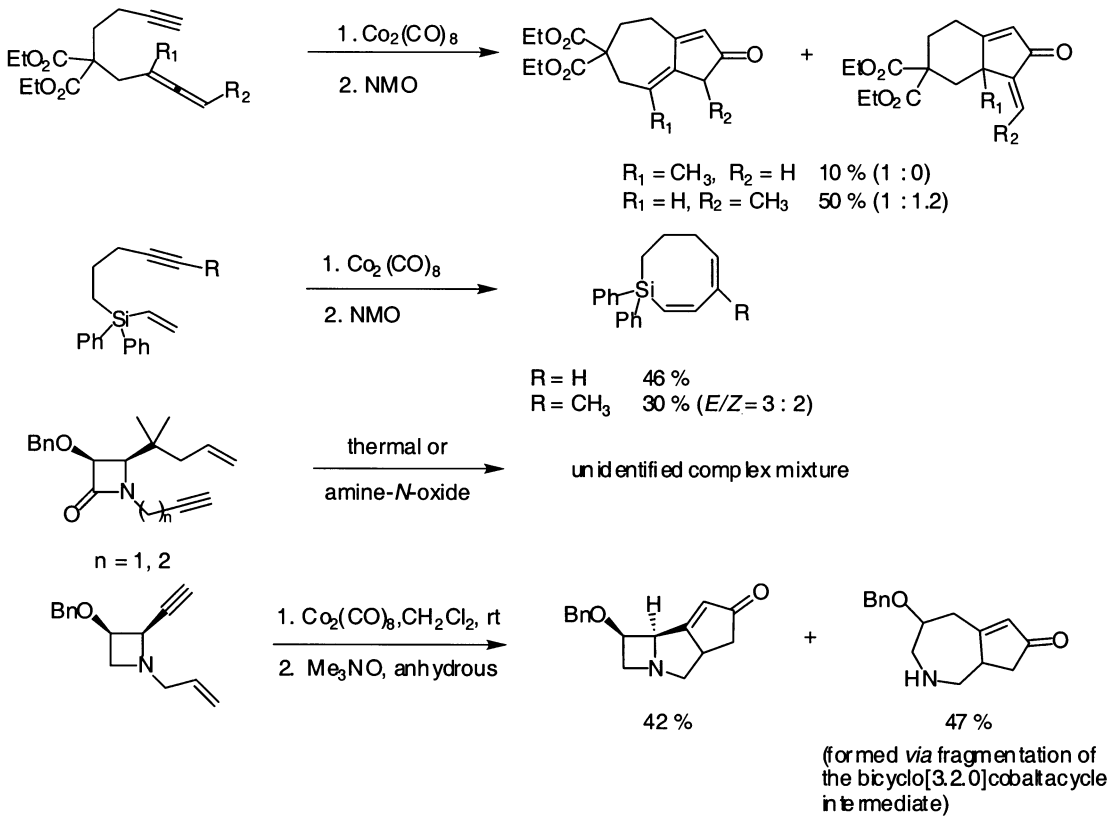
Received 16 November 2000; revised 11 December 2000; accepted 13 December 2000

Abstract—The dicobalthexacarbonyl alkyne complex of a series of enynes templated on aromatic rings has been shown to undergo the Pauson–Khand reaction to generate medium-sized rings.

As amply demonstrated in the literature, transition metal-based cycloaddition reactions have become an indispensable means to prepare complex synthetic targets often from simple starting materials.[1–4] For example, transition metals have provided an avenue for the facile construction of medium-sized (ring size = 8–11) and large-sized (ring size ≥ 12) macrocycles, which would have been difficult to achieve, if at all, using the traditional methods.[3] This facility is derived from their ability to serve as templates, via coordination and



Scheme 1.

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0040-4039/01/$ - see front matter
PII: S0040-4039(00)02299-1

subsequent reaction to form rings and at the same time alleviating the energy barrier associated with ring closures. One that has gained immense popularity and high synthetic value is the ruthenium-catalyzed olefin metathesis reactions, where a wide variety of cycloadducts of varying ring sizes have been prepared since its discovery.[5–7] We now report the utility of intramolecular Pauson–Khand cyclizations[4] for the syntheses of medium-sized cyclic compounds in a limited number of cases (ring size = 7, 10–12).

The only account of medium-sized ring formation using the Pauson–Khand reaction was an observation by Cazes, where a seven-membered ring was formed from the reaction of 1,2-dien-8-ynes (Scheme 1).[8] Interestingly, some reports describe the unexpected formation of seven- and eight-membered rings from enynes under the Pauson–Khand cyclization conditions. Instead of the normal [2+2+1]-cycloadduct, an eight-membered dienylsilane cycloisomerization adduct was obtained by Saigo from the cyclizations of 3-sila-1,7-enynes under the Pauson–Khand reaction conditions (Scheme 1).[9] On the contrary, in a study on the use of the Pauson–Khand cyclization as an entry to fused tricyclic 2-azetidinones by Alcaide, attempts at generating larger central ring systems (seven- or eight-membered) proved unsuccessful.[10] On the other hand, the reaction of an *N*-allylated and C_1-propargylated azetidine under the Me_3NO-promoted conditions yielded a seven-membered azepine, in addition to the anticipated azetidine-fused bicyclopentenone product (Scheme 1).[10] Formation of the larger ring presumably resulted from fragmentation of the expected cycloadduct. To date no medium-sized ring systems have been generated where the reactive groups are more than five atoms apart in the acyclic precursor using a Pauson–Khand reaction.[11]

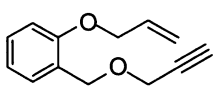
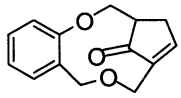
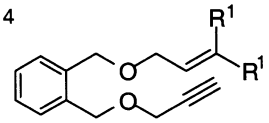
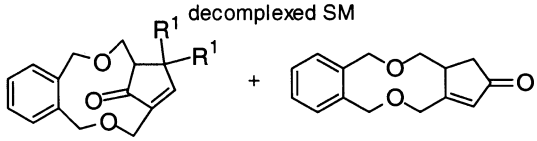
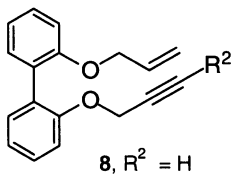
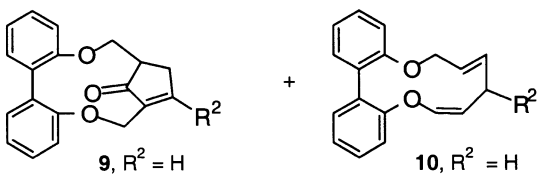
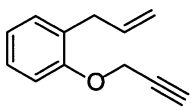
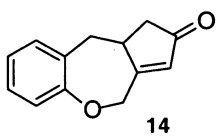
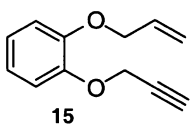
In order to minimize conformational mobility, we initiated our studies with substrates that were anchored into a rigid system, for example, one bearing an aromatic ring. In such systems, the reacting moieties are in close proximity to allow for a more facile cyclization. In effect, cyclization can be achieved before side reactions, such as decomplexation, oxidation or dealkylation could occur.

Results from our studies under a variety of cyclization conditions are summarized in Table 1.[12] The dicobalthexacarbonyl complex of 1,10-enyne **1** underwent cyclization to form a 10-membered bridged macrocycle. Moderate yields of the bridged enone **2** were obtained under the NMO- and thermally-promoted cyclizations (entries 1 and 3). In our efforts to improve the yields of this cycloadduct, enyne **1** was also subjected to the Me_3NO-promoted (entry 2) and cyclohexylamine-assisted thermal cyclization conditions (entry 4). However, no significant amounts of Pauson–Khand cycloadducts were noted from these reactions and mainly decomplexed starting materials were observed. Conversely, moderate yields of a 1.3:1 ratio of 11-membered bridged (**4**) and 10-membered fused (**5**) macrocyclic enones were observed from reactions of the dicobalthexacarbonyl complexed-enyne **3** (entries 5 and 7). Similar yields were obtained from the Me_3NO-promoted cyclization (entry 6). However, only the decomplexed starting enyne was recovered from the cyclohexylamine-assisted thermal version (entry 8). Interestingly, formation of the 10-membered fused macrocycle was favored under the former conditions (entry 6). Unsymmetrically substituted alkynes generally prefer to react in a manner which orients the larger substituent in the incipient α-position of the cyclopentenone.[13–15] However, formation of both regioisomeric products is observed if the middle ring is large enough to accommodate the strain associated with the bridging rings and the bridgehead double bond. Meanwhile, catalyses using rhodium (1–2 mol% $[RhCl(CO)_2]_2$, 0.05–0.008 M Bu_2O, 130°C, 1 atm CO)[16] or cobalt (10 mol% $Co_2(CO)_8$, 0.10 M DME, 60°C, 1 atm CO)[17] failed to effect the desired cyclizations. In both cases, enyne **3** was recovered, albeit a higher amount of starting material was observed from the latter conditions. Very small amounts of starting material (3–11%), in addition to the depropargylated starting material (8%) were obtained from the rhodium-catalyzed conditions. The catalyst had presumably decomposed before the reactive moieties were able to be in close proximity to react.

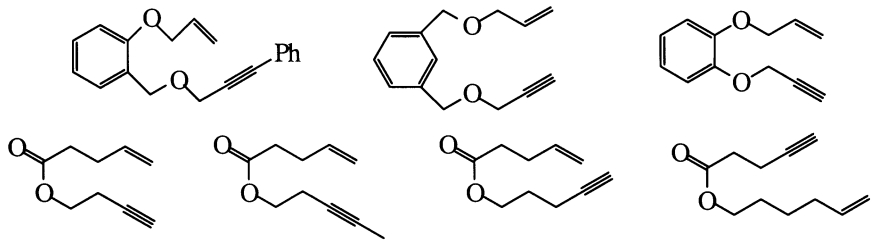
Meanwhile, cyclizations with the cyclopropylidene analogue **6** also gave similar yields of bridged enone **7** (entries 9 and 10 versus 5–7). We initially speculated that the enhanced reactivity of the methylenecyclopropyl group in the Pauson–Khand reaction could improve the efficiency of the cyclization.[18] Varying the reaction temperatures showed no apparent effect in the cyclization efficiency (entries 9 and 10). It should be noted that the steric requirements imposed by the cyclopropyl moiety led to the exclusive formation of the 11-membered bridged enone **7** (entries 9 and 10 versus 5–7). None of the normal Pauson–Khand regioisomeric cycloadduct was observed.

It was further envisioned that enynes templated on 2,2′-biphenol system could bring the reacting groups in a closer proximity to one another. Cyclization of this system indeed provided much improved yields of the medium-sized macrocycles than the monocyclic templated systems. Under the NMO-promoted conditions, a 1.6:1 ratio of the 11-membered bridged enone **9** and the 1,4-diene **10** was obtained in reactions promoted by NMO (entry 11). Interestingly, the 1,4-diene was generated exclusively under the thermal conditions, with (entry 13) and without cyclohexylamine (entry 12). Diene **10** presumably arises from β-elimination of the intermediate cobaltacycle rather than carbonyl insertion.[19] On the other hand, 11-membered bridged enone **9** was solely formed under the Me_3NO-promoted reaction (entries 14–16). The yields were comparable from cyclizations under different reaction concentrations (entry 14 versus 15) and reaction atmospheres (entry 14 versus 16). Likewise, rhodium-catalyzed cyclizations of enyne **8** only provided 7% of depropargylated starting material.[16] Finally, a change in the substituent on the alkynyl moiety (R^2 = Me, TMS) was found to be detrimental to the ease of cyclization of these substrates. Both NMO- (entry 17) and thermally-promoted cycliza-

Table 1. Intramolecular Pauson–Khand reaction for the synthesis of medium-sized macrocycles

Entry[a]	Substrate[b]	Conditions[c]	Product(s) (% Yield)
			
	1		**2**
1		**A**	31
2		**B**	decomplexed SM
3		**C**	31
4		**D**	decomplexed SM
	3, $R^1 = R^1 = H$		 **4**, $R^1 = R^1 = H$ + **5**
5		**A**	24 (1.2 : 1)
6		**B**	27 (1 : 2.4)
7		**C**	26 (1.4 : 1)
8		**D**	decomplexed SM
	6, $R^1 = R^1 = CH_2$		**7**, $R^1 = R^1 = CH_2$
9		**A**[d]	27
10		**A**[e]	26
	 **8**, $R^2 = H$		 **9**, $R^2 = H$ + **10**, $R^2 = H$
11		**A**	32 / 18
12		**C**	– / 71
13		**D**[f]	– / 65
14		**B**[g]	48 / –
15		**B**[g]	40 / –
16		**B**	45 / –
17	**11**, $R^2 = CH_3$	**A** or **C**	decomplexed SM
18	**12**, $R^2 = TMS$	**A** or **C**	decomplexed SM
	 **13**		 **14**
19		**A**	14
20		**C**	15
	 **15**		
21		**A** or **C**	decomplexed SM

(a) Entries 11-15, 17: 0.003 M substrate concentration; entries 16,18-21: 0.03 M substrate concentration, (b) as dicobalthexacarbonyl complexes. c) Conditions: **A**: 0.01 M CH_2Cl_2, 6 equiv NMO, N_2, rt; **B**: 0.003 M CH_2Cl_2, 5 equiv. of Me_3NO, Ar, -78 °C to rt; **C**: 0.01 M toluene, N_2, 65°C; **D**: 0.003 M 1,2-DCE, 10 equiv of cyclohexylamine, Ar, 85 °C, (d) enyne -$Co_2(CO)_6$ generated *in situ*, (e) enyne-$Co_2(CO)_6$ generated *in situ*, NMO added at 0 °C, then warmed to rt, (f) N_2 atmosphere, (g) O_2 atmosphere. SM = starting material.



Scheme 2.

tions (entry 18) provided only decomplexed starting materials. Furthermore, medium-sized ring formation from several other substrates was attempted unsuccessfully (Scheme 2) and only starting material was recovered from Pauson–Khand reactions under a variety of reaction conditions. Failure of these substrates to undergo cyclization under different conditions further supports the importance of restricted conformational mobility of the reacting moieties brought about by the rigid templates and the close proximity of the moieties to effect cyclization.

In summary, in a limited number of cases, formation of medium-sized fused or bridged tricyclic enones has been realized in the thermal (with or without an additive) and amine *N*-oxide-promoted Pauson–Khand cyclizations. Seven- and 10-membered fused and 10-membered and 11-membered bridged tricyclic enones were formed in modest to good yields from the cyclizations of the dicobalthexacarbonyl complexes of the corresponding enynes templated on aromatic rings. These provide the first examples of the potential utility of this cyclization in the formation of medium-sized macrocycles from enynes whose reacting unsaturated groups are separated by five or more atoms. The steric encumbrance imposed by the cyclopropyl group in a 1,11-cyclopropylidenyne favored the exclusive formation of the 11-membered bridged regioisomeric product. In addition, the difficulty in cyclization which arises from an internally substituted alkyne is significant enough to hinder the desired cyclizations in these systems.

Acknowledgements

Support for this work was provided by the National Science Foundation and donors to the Krafft Research Fund.

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11. Lovely recently described the synthesis of seven- and eight-membered rings using the Pauson–Khand reaction on an aromatic template (Lovely, C. A.; Wayland, B. *Book of Abstracts*, 220th ACS National Meeting, Washington, DC, August 20–24, 2000; American Chemical Society: Washington, DC, ORGN 349); however, no yields were reported.
12. **Enone 2**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.60 (dd, $J=2.6$, 2.2 Hz, 1H, C(O)C=CH), 7.22 (ddd, $J=7.7$, 7.7, 1.3 Hz, 1H, 5-Ph*H*), 7.21 (dd, $J=7.7$, 1.3 Hz, 1H, 3-Ph*H*), 6.91 (ddd, $J=8.3$, 7.2, 1.0 Hz, 1H, 4-Ph*H*), 6.82 (dd, $J=8.3$, 0.6 Hz, 1H, 6-Ph*H*), 4.54 (ABdd, $J_{AB}=12.1$, $J=1.3$, 1.0 Hz, 1H, OC*H*HCHCH$_2$), 4.51 (ABd, $J_{AB}=9.9$, $J=1.3$ Hz, 1H, OCH*H*C=CH), 4.48 (AB, $J_{AB}=10.8$ Hz, 1H, PhC*H*HO), 4.39 (ABd, $J_{AB}=9.9$, $J=2.9$ Hz, 1H, OC*H*HCCH$_2$), 4.20 (AB, $J_{AB}=10.8$ Hz, 1H, 6-PhCH*H*O), 4.06 (AB, $J_{AB}=12.4$ Hz, 1H, OCH*H*C=CH), 2.97 (ABddd, $J_{AB}=18.5$, $J=6.4$, 2.2, 1.9 Hz, 1H, C=CHC*H*H), 2.71 (ABd, $J_{AB}=18.5$, $J=3.5$ Hz, 1H, C=CHC*H*H), 2.66 (dddd, $J=6.4$, 2.3, 1.9, 0.6 Hz, 1H, C(O)C*H*CCH$_2$). Anal. calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.02; H, 6.19. **Enone 4**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66 (dd, $J=2.2$, 2.2 Hz, 1H, C=C*H*CH$_2$), 7.32 (dd, $J=7.7$, 1.9 Hz, 1H, 6-Ph*H*), 7.29 (ddd, $J=7.7$, 7.3, 1.6 Hz, 1H, 5-Ph*H*), 7.22 (ddd, $J=7.3$, 7.3, 1.9 Hz, 1H, 4-Ph*H*), 7.15 (dd, $J=7.3$, 1.3 Hz, 1H, 3-Ph*H*), 4.73 (AB, $J_{AB}=10.5$ Hz, 1H, 1-PhC*H*HO), 4.60 (AB, $J_{AB}=9.9$ Hz, 1H, 2-PhCH*H*O), 4.55 (ABd, $J_{AB}=12.1$, $J=0.6$ Hz, 1H, OC*H*HC=), 4.28 (AB, $J_{AB}=9.9$ Hz, 1H, 2-PhC*H*HO), 4.27 (AB, $J_{AB}=10.8$ Hz, 1H, 1-

PhCH*H*O), 4.02 (AB, J_{AB}=11.8 Hz, 1H, OC*H*HC=CH), 4.00 (ABd, J_{AB}=10.8, J=2.3 Hz, 1H, OC*H*HCHCH$_2$), 3.94 (ABd, J_{AB}=10.8, 2.5 Hz, 1H, OCH*H*CHCH$_2$), 2.85 ABddd, J_{AB}=18.8, J=6.4, 1.6, 1.2 Hz, 1H, C=CHC*H*H), 2.62 (ABd, J_{AB}=18.8, J=1.5 Hz, 1H, C=CHCH*H*), 2.55–2.58 (m, 1H, CH$_2$C*H*CH$_2$). Anal. calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: 73.49; H, 6.58. **Enone 5**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.50 (br d, J=7.7 Hz, 1H, 6-Ph*H*), 7.38 (ddd, J=7.7, 7.7, 1.3 Hz, 1H, 5-Ph*H*), 7.23 (ddd, J=7.7, 7.7, 1.3 Hz, 1H, 4-Ph*H*), 7.13 (dd, J=7.7, 1.3 Hz, 1H, 3-Ph*H*), 6.57 (d, J=2.9, 1H, COC*H*=C), 4.67 (AB, J_{AB}=12.8 Hz, 1H, 1-PhC*H*HO), 4.66 (AB, J_{AB}=11.7 Hz, 1H, 2-PhC*H*HO), 4.53 (AB, J_{AB}=12.8 Hz, 1-PhCH*H*O), 4.45 (Abdd, J_{AB}=11.8, J=1.0, 1.0 Hz, 1H, OC*H*HC=CH), 4.19 (AB, J_{AB}=12.1 Hz, 1H, 2-PhCH*H*O), 4.18 (AB, J_{AB}=12.1 Hz, 1H, OCH*H*C=CH), 3.94 (ABd, J_{AB}=10.8, J=2.6 Hz, 1H, OC*H*HCHCH$_2$), 3.43 (ABd, J_{AB}=10.8, J=1.6 Hz, 1H, OCH*H*CHCH$_2$), 2.91–2.95 (m, 1H, C*H*CH$_2$CO), 2.43 (d, J=4.8 Hz, 1H, CHC*H*HCO), 2.42 (d, J=2.6 Hz, 1H, CHCH*H*CO). Anal. calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.50; H, 6.63. **Enone 7**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.14–7.34 (m, 5H), 4.78 (AB, J_{AB}=10.6 Hz, 1H), 4.63 (AB, J_{AB}=10.0 Hz, 1H), 4.57 (AB, J_{AB}=11.8 Hz, 1H), 4.31 (AB, J_{AB}=10.0 Hz, 1H), 4.28 (AB, J_{AB}=10.6 Hz, 1H), 3.99 (AB, J_{AB}=12.4 Hz, 1H), 3.89 (d, J=2.4 Hz, 2H), 2.22 (t, J=2.4 Hz, 1H), 1.17–1.25 (m, 2H, Cpr-H), 0.98–1.12 (m, 2H, Cpr-H). **Enone 9**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.94–7.34 (m, 9H, 8 aromatic H and C=CH), 4.88 (ABd, J_{AB}=11.2, J=2.4 Hz, 1H, OC*H*HCH), 4.84 (AB, J_{AB}=11.7 Hz, 1H, OCH*H*C=C), 4.58 (AB, J_{AB}=11.7 Hz, 1H, OCH*H*C=C), 4.19 (ABd, J_{AB}=10.7, J=1.5 Hz, 1H, OC*H*HCH), 2.68 (ABd, J_{AB}=19.1 J=6.3 Hz, 1H, CHC*H*H), 2.48 (br dm, J=6.8 Hz, 1H, CH$_2$C*H*CH$_2$), 2.35 (ABd, J_{AB}=19.0, 2.0 Hz, 1H, CHCH*H*). Anal. calcd for $C_{19}H_{16}O_3\cdot 0.4H_2O$: C, 76.18; H, 5.38. Found: C, 76.26; H, 5.61. **1,4-Diene 10**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (m, 2H, aromatic H), 7.17 (m, 3H, aromatic H), 7.04 (ddd, J=6.3, 6.3, 6.3 Hz, 2H, aromatic H), 6.93 (d, J=8.3 Hz, 1H, aromatic H), 6.38 (dt, J=6.4, 2.0 Hz, 1H, OC*H*=CH), 5.83 (ddd, J=15.1, 6.4, 6.4 Hz, 1H, OCH$_2$C*H*=CH), 5.62 (dtd, J=15.1, 6.8, 6.8 Hz, OCH$_2$CH=C*H*), 4.87 (ddd, J=6.0, 6.0, 4.7 Hz, 1H, OCH=C*H*), 4.60 (dd, J=12.1, 7.3 Hz, 1H, OC*H*H), 4.39 (dd, J=12.2, 7.3 Hz, 1H, OCH*H*), 2.70 (ddd, J=17.1, 4.5, 4.5 Hz, 1H, OCH=CH-C*H*H), 2.64 (ddd, J=17.1, 5.8, 5.8 Hz, 1H, OCH=CHCH*H*). Anal. calcd for $C_{18}H_{16}O_2\cdot 0.4H_2O$: C, 79.62; H, 5.94. Found: C, 79.87; H, 6.24. **Enone 14**: ^{1}H NMR (500 MHz): δ 7.30 (ddd, J=7.3, 1.2, 1H, 4-Ph*H*), 7.28 (dd, J=7.3, 1.2, 1H, 3-Ph*H*), 7.10 (dd, J=7.3, 1.2, 1H, 6-Ph*H*), 7.08 (ddd, J=7.3, 7.3, 1.2, 1H, 5-Ph*H*), 6.06 (s, 1H, C=C*H*CO), 5.10 (AB, J_{AB}=14.3, 1H, OC*H*H), 4.44 (AB, J_{AB}=14.3, 1H, OC*H*HC), 3.08 (m, 1H, PhCH$_2$C*H*), 2.95 (ABd, J_{AB}=14.0, J=9.2, 1H PhC*H*HCH), 2.94 (ABd, J_{AB}=14.0, J=6.4, 1H, PhCH*H*CH), 2.80 (ABd, J_{AB}=18.8, J=6.7, 1H CHC*H*HCO), 2.24 (ABd, J_{AB}=18.8, J=2.9, 1H, CHCH*H*CO). Anal. calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.00. Found: C, 77.70; H, 6.08.

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