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Cyclopropyl Building Blocks for Organic Synthesis, 131.[1] Palladium-Catalyzed Bicyclization with Carbonyl Insertion of Alkenyl-Tethered Propargyl Carbonates Towards a Scalable Synthesis of Various 2-(Bicyclo[3.1.0]hex-1-yl)acrylates

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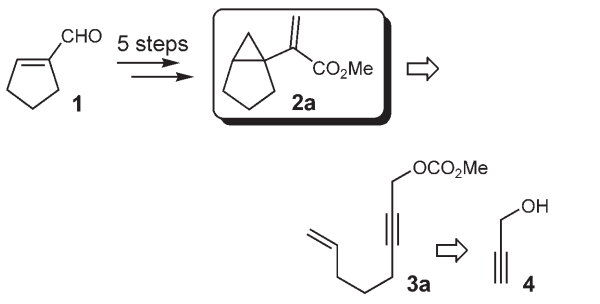
Abstract: The Pd-catalyzed 5-*exo-trig*-3-*exo-trig* cascade cyclization of 1,6-enynes with a propargyl carbonate terminus offers the shortest synthetic route to variously substituted 2-(bicyclo[3.1.0]hex-1-yl)acrylates, a novel class of prospective monomers for low-shrinkage polymers. To apply this reaction to large-scale preparations of the said bicyclic acrylates, a flexible Pd catalyst system with tunable reactivity has been developed. The dependence of the product and diastereomer distribution on both the reaction conditions, including the type of palladium catalyst used, and on the nature of the substrate has been investigated. A variety of methyl 2-(bicyclo[3.1.0]hex-1-yl)acrylates and parent carboxylic acids as well as some of their derivatives of potential interest towards a technical application were prepared on a multigram scale. A general large-scale synthesis of the cyclization precursors bearing one or two carbonyl groups in the tether is also disclosed.

Keywords: bicyclic vinylcyclopropanes; carbonylations; cycloisomerizations; homogeneous catalysis; palladium catalysts; ring strain

Introduction

A manifold of transition metal-catalyzed enyne cycloisomerizations has emerged during the last decade, and has opened a short and atom-economical access to diverse mono-, bi- and oligocyclic skeletons coming along with a remarkable increase in structural complexity.[2] Several recently reported successful examples of large-scale adaptations of such transformations[3] encouraged us to employ this attractive methodology in the development of a significantly improved approach to diverse analogues of 2-(bicyclo[3.1.0]hex-1-yl)acrylates[4] as novel monomers for low-shrinkage polymers in composites for dental materials.

Recent work in our group has shown that methyl 2-(bicyclo[3.1.0]hex-1-yl)acrylate[5] (**2a**) has a sufficiently high rate of polymerization going along with a rather low shrinkage and thus would be feasible for actual applications in dentistry.[6] We therefore conceived a shorter and more efficient approach to methyl 2-(bicyclo[3.1.0]hex-1-yl)acrylate (Scheme 1) which at the same time would be applicable towards the preparation of diverse, in terms of substitution



Scheme 1. Previous[5] and newly conceived synthesis of methyl 2-(bicyclo[3.1.0]hex-1-yl)acrylate.

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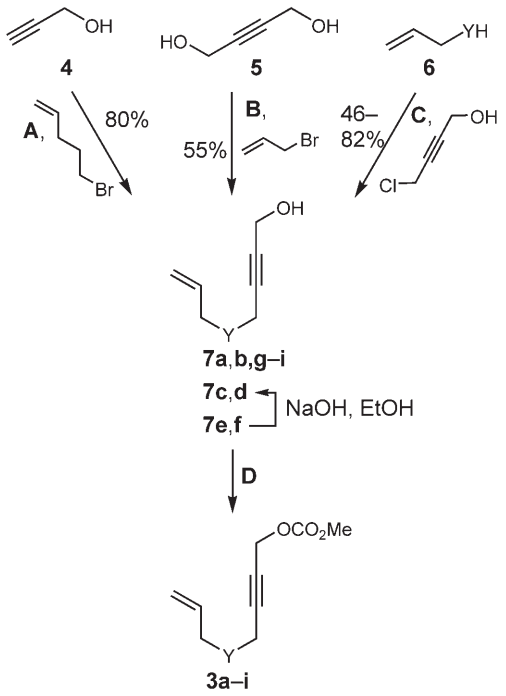
pattern and molecular weight, alkyl bicyclo-[3.1.0]hexylacrylates. Towards these, the Pd-catalyzed 5-*exo-trig*-3-*exo-trig* cascade cyclization of 1,6-enynes with a propargyl carbonate terminus, first reported by Grigg et al.[7] in 1996 and, not long after, detailed by Oppolzer et al.,[8] offers the shortest route. However, in order to be able to perform this bicyclization on a multigram scale, viable procedures for large-scale preparations of the respective acyclic 1,6-enynes as precursors would first have to be developed and, secondly, the scope and limitations of the said Pd-catalyzed bicyclization would have to be further investigated. Here we disclose an improved palladium catalyst cocktail which, with reasonably low loading, brings about a multigram scale cyclization-carbonylation cascade of various 1,6-enynes to the corresponding bicyclo[3.1.0]hexylacrylates.

Results and Discussion

Synthesis of 1,6-Enyne Cyclization Precursors

The preparation of the parent hept-6-en-1-ynylcarbinol **7a** on a multigram scale is well documented.[9] Thus, after two-fold deprotonation of propargyl alcohol (**4**) with lithium amide in liquid ammonia, alkylation with 5-bromopent-1-ene occurs selectively at the terminal carbon to afford **7a** in good yield (80%). Its 4-oxa-analogue **7b** could also be prepared on a multigram scale, though in moderate yield (55%), by alkylation of 2-butyne-1,4-diol (**5**) with allyl bromide in the presence of sodium hydride after appropriate modification of a previously published protocol.[10] Although the 1,6-enynes with a nitrogen atom in the tether are also easily accessible and have been well investigated in terms of various metal-catalyzed enyne cyclizations,[2,7,8] they were not considered here for technical reasons.[11]

Several successful syntheses of alkenyl-tethered propargyl carbonates of type **3e–i** with 1,6-enyne features (Scheme 2), by alkylation of C–H acidic compounds (e.g., allylditosylmethane[8] or dimethyl allylmalonate[12]) with 4-(methoxycarbonyloxy)but-2-ynyl halides have recently been published. However, it turned out to be rather problematic to extend this approach to a whole range of β-dicarbonyl compounds. Thus, upon attempted alkylation of diethyl allylmalonate (**6g**) with both 4-(methoxycarbonyloxy)but-2-ynyl chloride and iodide, the yield of the respective carbonate **3g** did not exceed 55%. Irrespective of the reasons for this behavior, the direct alkylation of 2-allyl-1,3-dicarbonyl compounds with the easily accessible 4-chlorobut-2-yn-1-ol[13] was tried. Surprisingly, a previously reported procedure,[14] after appropriate modifications, was found to furnish a wide variety of substituted ω-pentenylpropargyl alcohols **7c–i** in fair



Scheme 2. Synthesis of the 1,6-enyne cyclization precursors **3a–g**. *Reagents and conditions:* **A:**[9] $LiNH_2$, NH_3, THF, then 5-bromopentene, −34 to 20 °C, 12 h; **B:** NaH, DMF, THF, 64 °C, 1 h, then allyl bromide, 64 °C, 2 h; **C:** LiOH, 20 mol% LiI, THF, 64 °C, 30 min, then 4-chloro-2-butyn-1-ol, 64 °C, 3 h (GP 1A), then NaOH, EtOH, 64 °C, 2 h (GP 1B), or DBU, 20 mol% LiI, THF, 25 °C, 24 h; **D:** NEt_3, 5 mol% DMAP, $ClCO_2Me$, −10 to −5 °C, 1.5 h (GP 2). For further details, see Table 1.

to good yields (46–82%, Scheme 2, Table 1). Indeed, deprotonation of a β-dicarbonyl compound with anhydrous lithium hydroxide instead of its monohydrate as originally reported, afforded a more reactive enolate, which smoothly and chemoselectively (exclusive *C*-alkylation) reacted with 4-iodobut-2-yn-1-ol, generated *in situ* from the corresponding chloride in the presence of a catalytic amount of lithium iodide. Moreover, a subsequent retro-Claisen deacylation per-

Table 1. Synthesis of bicyclization precursors **3a–i**.

Entry		Y	Yield [%]	
			7	**3**
1	**a**	CH_2	80[8]	94
2	**b**	O	55	92
3	**c**	CHCOMe	81	96
4	**d**	$CHCO_2Et$	75	93
5	**e**	$C(COMe)_2$	70	91
6	**f**	$C(CO_2Et)COMe$	80	94
7	**g**	$C(CO_2Et)_2$	83	96
8	**h**	$C(CO_2Et)COPh$	64	82
9	**i**	$C(CO_2Et)CONaphth$-2-yl	46	78

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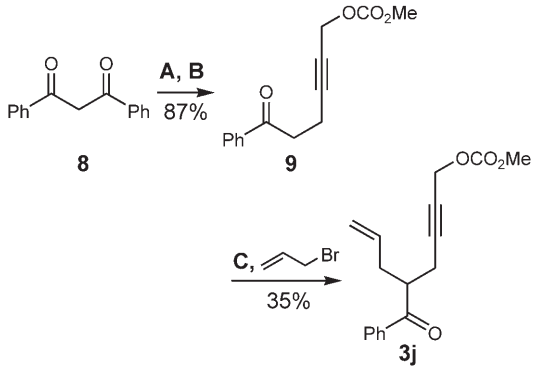
formed just by gradual addition of one equivalent of alcoholic sodium hydroxide solution to the refluxing reaction mixture, after the alkylation of the corresponding 1,3-diketone **6e** or β-keto ester **6f**, furnished the respective 5-monosubstituted oct-7-en-2-yn-1-ols **7c** and **d** also in good yields (81 and 75%, respectively). The same retro-Claisen reaction, however, is responsible for the reduced yields of compounds **7h** and **i** bearing more electrophilic aroyl keto groups; in both cases significant amounts of the by-product **7d** along with the corresponding starting material **6h** and **i** were found in the reaction mixture. The more sterically congested 1,1-dibenzoylbut-3-ene could not be alkylated with 4-chlorobut-2-yn-1-ol at all, probably due to steric reasons. Since all attempts to remove the ethoxycarbonyl group from the compounds **7h** failed, the benzoyl-substituted enyne **3j** was prepared, albeit in poor overall yield (30%), along an alternative route (Scheme 3), i.e., by alkylation of dibenzoylmethane (**8**) with 4-chloro-2-butyn-1-ol with subsequent debenzylation and then allylation of the resulting **9**.



Scheme 3. Synthesis of the 1,6-enyne cyclization precursor **3j**. *Reagents and conditions:* **A:** LiOH, 20 mol% LiI, THF, 64°C, 30 min, then 4-chloro-2-butyn-1-ol, 64°C, 3 h, then NaOH, EtOH, 64°C, 2 h (GP 1B). **B:** NEt_3, 5 mol% DMAP, $ClCO_2Me$, −10 to −5°C, 1.5 h (GP 2). **C:** LiHMDS, THF, −70°C, 2 h, then DMPU (1 equiv.), allyl bromide (1.5 equivs.), −70°C to 20°C, 16 h.

For the reproducible alkylation of diethyl allylmalonate (**6g**), however, lithium hydroxide had to be replaced with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[15] to afford the respective 1,6-enyne **7g** in good yield (83%). Yet, the presence of the lithium iodide is crucial for success, as in the absence of this Lewis acid the base strength of DBU had been shown not to be sufficient to deprotonate alkyl malonates.[16]

The thus prepared alkenyl-tethered propargyl alcohols **7a–i**, were smoothly converted with methyl chloroformate in the presence of 5 mol% of DMAP and triethylamine into the corresponding carbonates **3a–i** in almost quantitative yields, which in some cases rendered an additional purification of the product obsolete. It turned out to be essential to use the acylation catalyst DMAP, and to rigorously control the reaction conditions, in order to exclude formation of any carbonates with two propargyl residues (that had been observed in the absence of DMAP, or at increased temperatures), which even in trace amounts would drastically decrease the activity of the palladium catalyst (see below).

Palladium-Catalyzed Bicyclization-Carbonylation Reactions of Alkenyl-Tethered Propargyl Carbonates 3a–j

Initially, the catalytic system previously reported by Oppolzer et al.,[8] consisting of Pd_2dba_3 and tris(2-furyl)phosphine (TFP) in a 1:4 molar ratio, was tested. Tris(2-furyl)phosphine had been declared the ligand of choice for Pd(0)-catalyzed 5-*exo-trig*-3-*exo-trig* cascade bicyclizations of 1,6-enynes with a propargyl carbonate terminus for at least two reasons. The high nucleophilicity of the phosphine ligand facilitates initial formation of the allenyl-palladium species **10′** occurring by an S_N2' attack of the palladium(0) species onto the triple bond of **3** with simultaneous irreversible extrusion of carbon dioxide (Scheme 4). On the other hand, the small steric demand of this phosphine ligand facilitates the subsequent cyclization cascade, which during the 5-*exo-trig*-and 3-*exo-trig*-ring closure steps involves sterically congested transition structures. These features of the catalyst make the required cyclization cascade occur at room temperature without undesired side reactions, which could arise at increased temperatures from the intermediates **10′** or **11′**.

Indeed, the Pd_2dba_3/P(2-fur)$_3$ system at 5 mol% catalyst loading worked very well for the substrate **3g** with a *gem*-disubstituted carbon atom in the tether, yielding the corresponding bicyclic acrylate **2g** almost quantitatively, whereas the bicyclization of the non- and the monosubstituted precursors **3a** and **3d** did proceed to give **2a** and **2d** in good yields (about 70%) but contaminated with small amounts of inseparable by-products (for **2a**) and dibenzalacetone (for **2d**).

Therefore, other catalyst systems based on relatively inexpensive palladium acetate were screened.[17] Two systems, both applying two equivalents of tris(2-furyl)phosphine,[18] and one with trimethyl phosphite (**A**),[19] the other one with a quaternary ammonium bromide (**B**)[20,21] added as "reducing agent" for palladium(II), turned out to be appropriate.

The addition of trimethyl phosphate to the catalyst system **A** for the attempted bicyclization of the unbranched enynes **3a** and **b** was found to suppress the formation of palladium black, and thus prolonged the lifetime of the active catalyst. A more detailed investigation into the role of such additives showed that

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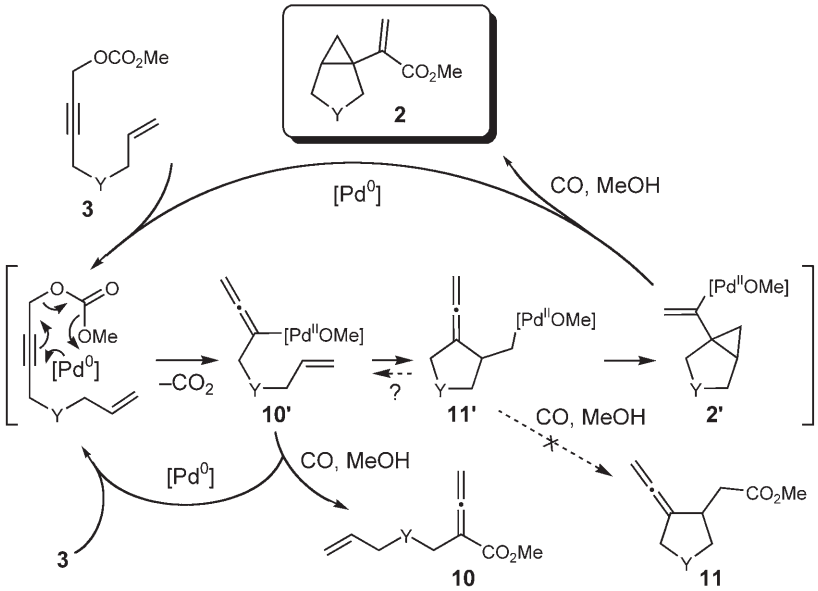

Scheme 4. General catalytic cycle for Pd-catalyzed cycloisomerization-carbonylation cascades of alkenyl-tethered propargyl carbonates.

they should have an affinity to the actual palladium catalyst, which is similar to or slightly exceeding that of the substrate 1,6-enyne. They have to find the delicate balance between inhibiting the aggregation of the dissolved catalyst to insoluble particles, as well as its coordination with a second molecule of the substrate or the product, and the retention of its catalytic activity for extended times.

With the catalyst system **A** (loading 2 mol % of palladium), the unsubstituted enynes **3a** and **b** were cleanly converted to acrylates **2a** and **b** in excellent yields (Table 2, entries 5 and 8). Remarkably, the products did not contain any significant contamination and could be separated from the catalyst just by flash chromatography to reach 98 % purity. This catalyst, however, turned out to be ineffective for the conversion of the enynes **3e–i** with a β-dicarbonyl moiety in the tether. Yet, with the modified catalyst cocktail **B**, the *gem*-dicarbonyl-substituted enynes **3e–i** were smoothly converted into the corresponding bicyclic acrylates **2e–i** in good yields (Table 2, entries 21, 22 and 24–26). Interestingly, the substrates **3a–d** and **j**, which do not feature a *gem*-disubstitution,[22] in the presence of catalyst **B** also yielded significant amounts of uncyclized allenecarboxylates **10a–d** originating from a propargylic rearrangement-carbonylation process.[23] With the bulky dopand 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) and under a slightly higher pressure of carbon monoxide (5 bar), the allenecarboxylate **10a** is formed from **3a** as the major product (Table 2, entry 2). In view of these results, the chemoselective conversions of 1,6-enynes **3c**, **d** and **j** bearing only one carbonyl group in the tether presented a particular challenge.

Whereas catalyst **B** with toluene as an additive achieved excellent yields of the bicyclic acrylates **2e–h** from the *gem*-disubstituted precursors **3e–h** even on a scale of 10–45 g (Table 2, entries 21, 22, 24 and 25), the bicyclizations of the precursors **3c**, **d** and **j** bearing only one functionality in the tether, in the presence of the catalyst **A** furnished a satisfactory yield and purity only in the case of the enyne **3d** (Table 2, entry 20). In order to solve the task to achieve reasonable yields of the mono-substituted products **2c**, **d** and **j**, a deeper insight into the mechanistic details of the bicyclization process was sought. A clue to understanding this could be expected from an analysis of the observation that, in several instances, diastereomerically enriched product mixtures were formed. To clarify the origin of this diastereoselectivity, the relative configurations of the diastereomers had to be assigned first.

Therefore, the diastereomers of **2c**, **d** and **j** were separated by column chromatography and analyzed by ^{1}H NMR spectroscopy including NOE measurements. In view of the chromatographic behavior and the spectral data, one could distinguish one series from the other as being characterized by higher R_f values (corresponding to lower dipole moments), larger chemical shift differences between the multiplets belonging to the protons *exo*-6-H and *endo*-6-H (H_b and H_a respectively, see Figure 1; the signals of the *endo*-protons are shifted upfield), and downfield shifts of the signals of 3-H. According to published results,[23] the first series was assigned to have the substituent at C-3 *endo*-positioned, presuming that both the *endo*- and *exo*-configured compounds **2c**, **d** and **j** adopt a boat-like conformation. This would be in ac-

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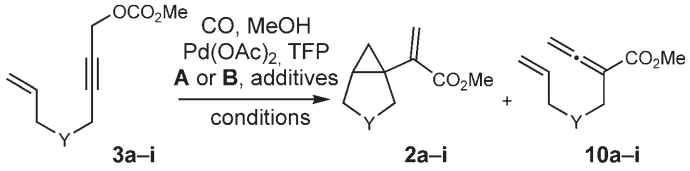
Table 2. Pd-catalyzed cycloisomerization-carbonylation cascade of propargyl carbonates **3a–j**.[a]



3a–i **2a–i** **10a–i**

Entry		Y	Catalyst System	Dopand	*P* [bar]	*t* [h]	Conv. [%]	Yield[b] of **2** [%]	*dr endo/exo* **2**	Yield of **10** [%]
1	**a**	CH_2	Ref. [8][c]	-	1	16	100	65	-	-
2	**a**	CH_2	**B**	BHT	5	12	100	24	-	50
3	**a**	CH_2	**B**	Ph_3PO	1	20	98	58	-	24
4	**a**	CH_2	**B**	norbornadiene	1	48	70	55	-	-
5	**a**	CH_2	**A**[d,e]	$OP(OMe)_3$[f]	1	16	100	99(94)	-	-
6	**b**	O	**B**	BHT	5	16	97	46	-	38
7	**b**	O	**B**	BHT	1	16	100	82	-	18
8	**b**	O	**A**[d,e]	$OP(OMe)_3$[f]	1	48	99	**87**	-	1
9	**c**	CHCOMe	**B**	BHT	5	12	65	30	1:1	30
10	**c**	CHCOMe	**B**[e]	camphor	1	45	100	68	3:2	22
11	**c**	CHCOMe	**A**	camphor	1	23	99	84(62)	5:3	5
12	**c**	CHCOMe	**A**	camphor[d]	1	18	100	87	2:1	3
13	**c**	CHCOMe	**A**[d,e]	$OP(OMe)_3$[f]	1	24	99	84	1:1	8
14	**c**	CHCOMe	**A**	toluene[g]	1	21	99	77	2:1	4
15	**c**	CHCOMe	**A**	DMPU	1	19	100	81	5:3	3
16	**c**	CHCOMe	**A**[e]	$(COPh)_2CH_2$	1	24	99	85(64)	3:2	6
17	**d**	$CHCO_2Et$	Ref. [8]	-	1	18	99	0(63)[h]	5:4	-
18	**d**	$CHCO_2Et$	**B**	toluene[g]	1	16	100	50	1:1	15
19	**d**	$CHCO_2Et$	**A**	Ph_2CO	1	72	89	88	3:2	-
20	**d**	$CHCO_2Et$	**A**[d,i]	$OP(OMe)_3$[f]	1	48	99	87(**69**)	1:1	<1
21	**e**	$C(COMe)_2$	**B**[e]	toluene[g]	1	48	100	**88**	-	1
22	**f**	$C(CO_2Et)COMe$	**B**[e]	toluene[g]	1	48	100	**91**	2:1	-
23	**g**	$C(CO_2Et)_2$	Ref. [8]	-	1	24	100	92	-	-
24	**g**	$C(CO_2Et)_2$	**B**[i]	toluene[g]	1	24	100	**86**	-	-
25	**h**	$C(CO_2Et)COPh$	**B**	toluene[g]	1	60	100	**84**	1:1	1
26	**i**	$C(CO_2Et)CONp$	**B**	BHT	1	24	99	**87**	1:1	1
27	**j**	CHCOPh	**A**	camphor	1	24	100	(60)	7:3	-

[a] Catalyst composition: **A:** 1 equiv. $Pd(OAc)_2$, 2.2 equivs. TFP, 1.1 equivs. $P(OMe)_3$, 1.1 equivs. additive; **B:** as **A**, but Me_4NBr instead of $P(OMe)_3$ was used. Catalyst loading: 3 mol%. BHT = 3,5-di-*tert*-butyl-4-hydroxytoluene, DMPU = *N*,*N*′-dimethylpropyleneurea, Np = naphth-2-yl, TFP = P(2-furyl)$_3$.

[b] Yield estimated on the basis of the ^1H NMR spectrum of the crude reaction mixture or by GC (for entries 1–7). Values in parentheses correspond to isolated yields of **2**. Isolated yield of product of the reaction performed for an at least 10 g scale is shown in bold.

[c] Catalyst composition: 1 equiv. $Pd_2(dba)_3$, 4 equivs. P(2-furyl)$_3$. Catalyst loading: 5 mol%.

[d] 2 equivs. with respect to Pd(0).

[e] Catalyst loading: 2 mol%.

[f] 5 equivs. with respect to Pd(0).

[g] 1 equiv. with respect to 1,6-enyne **3**.

[h] Isolated product **2d** contains ~5% of dibenzalacetone (dba) as an inseparable contaminant.

[i] Catalyst loading: 2.5 mol%.

cordance with the X-ray crystal structure of the parent bicyclo[3.1.0]hexane,[25] the experimentally observed coupling constants for 3-H in compounds **2c**, **d** and **j** (Figure 1 and Table 3) and the lack of any NOE between *endo*-6-H and *exo*-3-H in a selective 1D-NOE experiment. Hence, positive responses in the NOE experiment indicating interactions between 3-H and *endo*-6-H protons, which were observed for the other series of diastereomers, are indicative of their being *exo*-configured. In view of these assignments and additional NMR spectral features, the unsymmetrically *gem*-disubstituted bicyclo[3.1.0]hexane derivatives **2f**, **h** and **i** could also unambiguously be assigned (Table 3).

The chemical shifts of the protons *endo*-6-H within the whole set of bicyclo[3.1.0]hexane derivatives **2c–j**

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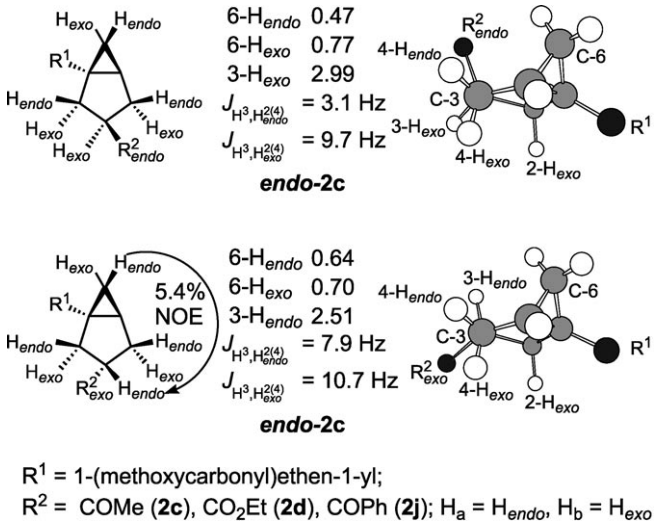

Figure 1. Assignment of the relative configuration of the diastereomeric 3-acylbicyclo[3.1.0]hexylacrylates **2c**, **d** and **j**.

are influenced by the anisotropy effect of the C=O groups on C-3 (Table 3). Thus, the downfield shift caused by the *endo*-substituent decreases in the order: COMe > CO_2R > COAr ≥ H (Table 3). The signals of the carbon atoms C-6 are also shifted downfield by *endo*-positioned substituents at C-3, especially strongly, when they are aroyl groups as in **2h**, **i** and **j** (Table 3).

According to these assignments, a clear preference for the formation of the bicyclic acrylates **2c**, **f** and **j** with an *endo*-positioned keto group can be noted. This behavior can be rationalized considering the relative energies of the four transition structures in the stereo-defining 5-*exo-trig* ring-closure step.

Hence, in the least complicated case of **2f**, the major diastereomer has a 3-acetyl group in the *endo*-position (Table 2, entry 22; Table 3, entries 8 and 9). Since there is roughly no steric difference between an acetyl and an ethoxycarbonyl group, the clear preference for the formation of the *endo*-acetyl diastereomer must be attributed to an attractive interaction between the acetyl carbonyl and the allenylpalladium moiety, which favors TS^3 over TS^2 as well as over TS^1 and TS^4 (Scheme 5), in which no electronic interaction is possible. The electronic interaction in TS^3 must even overcome the steric disadvantage that the boat-like conformation has compared to its chair-like counterparts. In the case of the 3-monosubstituted enynes leading to the bicyclic acrylates **2c**, **d** and **j**, the directing influence is also affected by the repulsive interaction of that substituent with the ligand environment of the palladium moiety, which is not compensated by an equally bulky second substituent in the tether as an ethoxycarbonyl group in the transition state leading to **2f**. Thus, taking into account the observed decrease of the diastereoselection in the above mentioned series from 7:3 for **2j** through 3:2 for **2c** to 1:1 for **2d**, the relative affinity of the differently substituted carbonyl groups to the palladium center apparently decreases in the order COPh > COMe > CO_2Et. Obviously, without such interactions, the bicyclization of the monosubstituted enynes **3c**, **d** and **j** would yield approximately 1:1 mixtures of the respective two diastereomers **2c**, **d** and **j**. However, such a lack of diastereoselectivity is observed only for the cyclizations of compounds **3h** and **i** (Table 2, entries 25 and 26), and also for **3d** in the presence of certain additives (Table 2, entries 18 and 20). Most probably, in the case of **3d**, TS^2 featured with the least repulsive interaction (R^2 = H) is slightly favored over TS^3 (least at-

Table 3. Influence of the substituents on C-3 on the chemical shifts of selected protons (H$_a$ refers to the *endo*-, H$_b$ to the *exo*-protons) and carbon atoms of the bicyclo[3.1.0]hexane core in compounds **2**.

Entry	**2**	R^2_{endo}	R^2_{exo}	6-H$_a$	6-H$_b$	3-H	C-6	C-3	R_f
1	**a**	H	H	0.63	0.62	1.22, 1.61	12.9	21.1	-
2	**b**	-O-		0.82	0.85	-	13.9	-	-
3	**c**	H	$COCH_3$	0.67	0.72	2.62	14.2	48.4	lower
4	**c**	$COCH_3$	H	0.35	0.72	3.06	16.3	51.5	higher
5	**d**	H	CO_2Et	0.64	0.70	2.51	13.9	40.0	lower
6	**d**	CO_2Et	H	0.47	0.77	2.99	16.2	51.7	higher
7	**e**	$COCH_3$	$COCH_3$	0.24	0.67	-	16.0	75.7	-
8	**f**	CO_2Et	$COCH_3$	0.50	0.76	-	16.4	67.1	lower
9	**f**	$COCH_3$	CO_2Et	0.36	0.68	-	16.4	67.0	higher
10	**g**	CO_2Et	CO_2Et	0.52	0.74	-	16.3	59.9	-
11	**h**	CO_2Et	COPh	0.50	0.69	-	16.5	64.1	lower
12	**h**	COPh	CO_2Et	0.88	0.83	-	18.1	65.1	higher
13	**i**	CO_2Et	CONaphth	0.55	0.72	-	16.5	64.3	lower
14	**i**	CONaphth	CO_2Et	0.96	0.85	-	18.1	65.3	higher
15	**j**	H	COPh	0.82	0.79	3.47	14.7	42.9	lower
16	**j**	COPh	H	0.69	0.77	4.02	16.9	46.5	higher

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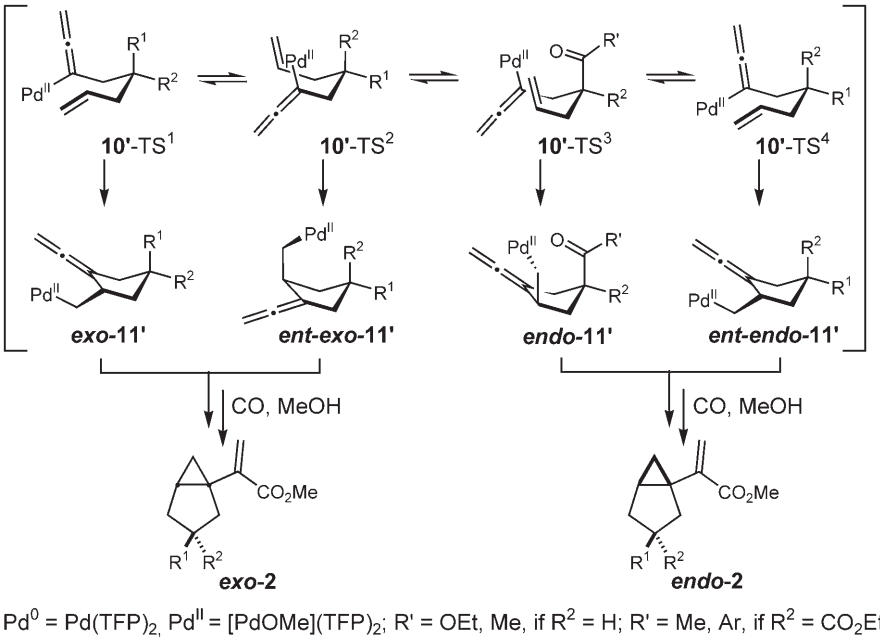
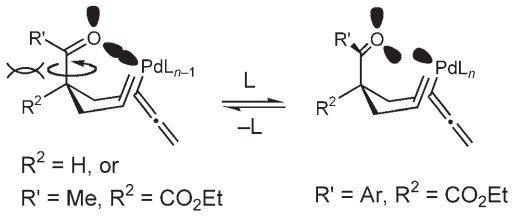


Scheme 5. Stereochemical aspects of the palladium-catalyzed cascade bicyclization.

tractive interaction for the most weakly interacting function CO_2Et), whereas TS^4 is slightly favored over TS^1 for steric reasons. In addition, the step **10′**→**11′** in the sequence (Scheme 4) may be reversible, as indicated by the fact that not even traces of the monocyclic allene derivative **11** have ever been found among the reaction products. This reversibility would then be responsible for some preferential formation of the thermodynamically more stable *exo*-isomer, if the rate of subsequent 3-*exo*-*trig*-ring closure (step **11′**→**2′**, Scheme 4) would be comparable with the rate of the retro-5-*exo*-*trig* process (step **11′**→**10′**).

The lack of diastereoselectivity in the case of **3h** and **i** can be rationalized by closer inspection of TS^3 (Scheme 6). An attractive overlap between the nonbonding orbital of the oxygen in the stereodefining carbonyl group and a vacant *d* orbital of palladium would occur if the system could adopt an appropriate conformation and this is not prevented by the repulsive interactions between the geminal functionalities



Scheme 6. Stereoelectronic aspects of the ring-closure step of 1,6-enyne precursors **3c**, **d**, **f** and **h–j** with two different substituents in the tether.

in the tether. This apparently is possible, if $R' \neq Ar$, or $R' = Ar$ and $R^2 = H$. In the other cases, the more bulky aryl group is forced out of the coplanarity with R^2 by the geminal substituent ($R^2 \neq H$).

The thus deduced affinity of the palladium catalyst for carbonyl groups triggered the idea to add a carbonyl compound to the catalyst cocktail to improve the yields of **2c** and **j**. Indeed, when camphor instead of trimethyl phosphate was used in catalyst **A** (Table 2, entry 12), the crude yield of the bicyclic acrylate **2c** was increased up to 87% and the yield of the allenecarboxylate by-product **10c** dropped to 3%. Use of 1 equivalent (with respect to Pd) of the more nucleophilic DMPU instead of camphor slightly decreased the yield and the diastereoselectivity for **2c**, and addition of the more bulky dibenzoylmethane, featuring a higher affinity for palladium, caused a further loss of diastereo- and chemoselectivity (Table 2, entries 15 and 16). As shown above, the addition of toluene (1 equivalent with respect to the 1,6-enyne **3**) can also be efficient to keep the catalyst appropriately active in solution for prolonged times (up to 72 h), and bring about the cascade bicyclization of the precursors **3e–h** to afford the target compounds **2e–h** in good isolated yields (84–91%), whereas an attempted cascade bicyclization of the methyl ester analogue of **3g** in the presence of the same catalyst, but without added toluene, gave the respective bicyclic acrylate in reasonable yield (63%) only with increased catalyst loading (5 mol%).[26] Addition of the more π-basic 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) achieved smooth bicyclization of **3i**, though a longer reaction

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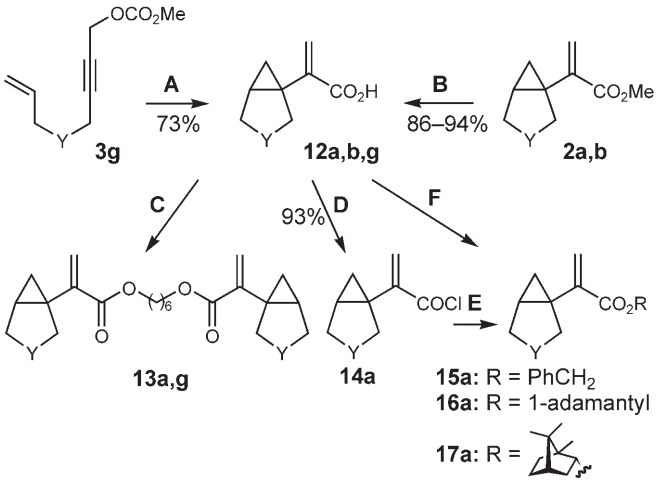
time was required (obviously, the higher the affinity of a dopand is to palladium, the lower is the activity of the catalyst obtained). Moreover, with BHT as a dopand, the bicyclization of **3g** could also be performed in aqueous media. Indeed, the above discussed order of affinities of Lewis bases to palladium, which follows the sequence BHT > α-aroylacetate ≥ toluene ≥ β-diketone ≈ β-keto ester ≥ β-diester > aryl ketone > ketone > ester, may be extended in terms of a further decrease of nucleophilicity in the sequence: MeOH > H_2O > AcOH. This means that acetic acid should be an appropriate co-solvent, if water is going to be used as the finally involved nucleophile, since the 1,6-enynes **3**, naturally, are not soluble in water.[27] Any solvent with a higher affinity to palladium would completely suppress the desired catalytic cycle.

Indeed, the cascade bicyclization of the 1,6-enyne **3g** smoothly proceeds in aqueous acetic acid in the presence of the BHT-doped palladium catalyst (3 mol%) affording the free acrylic acid **12g** in good isolated yield (73%). Since a selective hydrolysis of the acrylic ester function in **2d–i** in general cannot be achieved, the direct preparation of the free acid is essential for the potentially required further modification of the acrylic ester moiety in these bicyclo-[3.1.0]hexylacrylates. Thus **12g**, and also **12a**, obtained by hydrolysis of **2a**, were converted to some other the mono- and difunctional esters with the appropriate alcohols or benzyl chloride (Scheme 7, Table 4).



Scheme 7. Representative examples for modification of bicyclic acrylic acids **12a** and **g**: **A:** 3 mol% $Pd(OAc)_2$, 2.2 $P(2\text{-furyl})_3$, 1.1 Me_4NBr, 1.1 BHT (equivs. with respect to Pd), 60% aqueous AcOH, 1 bar CO, 25 °C, 24 h. **B:** $LiOH \cdot H_2O$, 70% aqueous acetone, 25 °C, 24 h. **C:** 1,6-Hexanediol, PPh_3, DEAD, THF, −70 to 25 °C, 3 h. **D:** $(COCl)_2$, CH_2Cl_2, DMF, 25 °C, 3 h. **E:** Alcohol, NEt_3, DMAP, CH_2Cl_2, 25 °C, 36 h. **F:** Benzyl chloride, K_2CO_3, KI, DMF, 25 °C, 24 h. For yields of esters **13** and **15**–**17** see the Table 5.

Table 4. Synthesis of bicyclic acrylic esters **13a**, **g, 15a–17a**.

Entry	Acid	Esterification partner	Method	Product	Yield [%]
1	**12a**	1,6-hexanediol	**C**	**13a**	84
2	**12g**	1,6-hexanediol	**C**	**13g**	86
3	**12a**	$PhCH_2Cl$	**F**	**15a**	90
4	**12a**	adamantan-1-ol	**E**	**16a**	76
5	**12a**	(*1S*)-(−)-borneol	**E**	**17a**	63

Conclusions

In conclusion, a flexible tuning of a palladium catalyst system to perform 5-*exo-trig*-3-*exo-trig* cascade cyclizations of 4-pentenyl-tethered propargyl carbonates with subsequent carbonylation and nucleophilic trapping on a decimolar scale in good yields has been achieved. The radical polymerization efficiencies of the new bicyclic acrylates **2b**, **d–i**, **13a** and 13**g**, each prepared on a multigram scale, were investigated and have been published elsewhere.[28]

Experimental Section

General

^1H NMR spectra were recorded on Bruker AM 250 (250 MHz), Varian Unity 300 (300 MHz) or Varian Inova 600 (600 MHz, NOE experiments) spectrometers. ^{13}C NMR spectra were recorded on Bruker AM 250 (62.9 MHz), Varian Unity 300 (75.6 MHz) and Varian Inova 500 (125.7 MHz) spectrometers. Multiplicities were determined by DEPT (distortionless enhancement by polarization transfer; Bruker), or by APT (attached proton test; Varian) measurements. The residual signal of $CHCl_3$ served as an internal standard. IR: Bruker IFS 66 (FT-IR) spectrometer, samples were measured as KBr pellets or oils between KBr plates. MS (EI, 70 eV) or MS (70 eV, DCI, NH_3): Finnigan MAT 95 spectrometer. Melting points: Büchi 510 capillary melting point apparatus, values are uncorrected. TLC: Macherey–Nagel pre-coated sheets, 0.25 mm Sil G/UV_{254}. Column chromatography: Merck silica gel 60 (70–230 mesh). Analytical gas chromatography: Varian CP-3800. Flash chromatography: Merck silica gel 60 230–400 mesh; the "dry column technique"[29] was applied. Elemental analyses were performed by the "Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen" with an elemental analyzer CHN-2000 (Leco). Starting materials and solvents: tetrahydrofuran (THF) was distilled from sodium/benzophenone. Methanol, toluene and methyl chloroformate were distilled under argon. Anhydrous dichloromethane was distilled from phosphorus pentoxide under nitrogen and stored over molecular sieves 3 Å. Triethylamine and pyridine were distilled over calcium hydride under nitrogen. Pentane, hexane, diethyl ether, *tert*-butyl methyl ether, anhydrous lithium hydroxide, lithium iodide, thionyl chloride, 2-butyne-1,4-diol,

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allyl bromide, allylmalonic acid diethyl ester, 4-*N,N*-dimethylaminopyridine (DMAP), palladium(II) acetate, tris(2-furyl)phosphine (TFP), trimethyl phosphite, trimethyl phosphate, tetramethylammonium bromide, 2,6-di-*tert*-butyl-4-methylphenol (BHT) were used as commercially available without further purification. Oct-7-en-2-yn-1-ol (**7a**),[9] 3-allylpentane-2,4-dione (**6e**),[30] ethyl 2-acetylpent-4-enoate (**6f**)[31] and ethyl 2-benzoylpent-4-enoate (**6h**)[32] were prepared as previously described. Abbreviations used: BHT = 3,5-di-*tert*-butyl-4-hydroxytoluene, dba = dibenzalacetone, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DEAD = diethyl azodicarboxylate, DMPU = *N,N'*-dimethylpropyleneurea, DMAP = 4-(*N,N*-dimethylamino)pyridine, HMDS = hexamethyldisilazane, TFP = tris(2-furyl)phosphine.

4-Chloro-2-butyn-1-ol[13]

In an oven-dried, 1-L three-necked flask fitted with a mechanical stirrer, a thermometer and a gas inlet with bubbler was placed under argon 2-butyne-1,4-diol (86.1 g, 1 mol). The flask was stoppered with a septum, and anhydrous triethylamine (140 mL, 1 mol) was added with stirring through a cannula. After the diol had completely dissolved, anhydrous dichloromethane (100 mL) was added, the mixture was cooled to 10 °C and thionyl chloride (75 mL, 1 mol) was added slowly within 1 h through a cannula with a syringe pump, while the vigorously stirred mixture was kept between 10 and 15 °C (ice/salt bath). The mixture was stirred with cooling for an additional 15 min, then the cooling bath was removed, and stirring was continued at ambient temperature overnight. Then it was cooled (ice/water bath) and diluted with anhydrous *t*-BuOMe (500 mL). The mixture was stirred with cooling for 1 h and then filtered. The cake on the filter was washed with *t*-BuOMe (3 × 100 mL). The solvents were evaporated, and the residual brown liquid (123 g) was "bulb-to-bulb" distilled (80–110 °C/0.1 mbar) to give 85 g of a colorless liquid. This was rectified under reduced pressure over a 30 cm Vigreux column affording *1,4-dichlorobut-2-yne* [yield: 22.6 g (18 %); bp 66–69 °C/23 mbar] and *4-chloro-2-butyn-1-ol* [yield: 56.4 g (54 %); bp 90–91 °C/13 mbar].

4-(2-Allyloxy)but-2-yn-1-ol (7b)

To a stirred suspension of NaH (120 mmol, 4.8 g of 60 % dispersion in oil) in anhydrous THF (50 mL) was gradually added 2-butyne-1,4-diol (**5**) (17.2 g, 200 mmol) dissolved in anhydrous DMF (50 mL). After stirring under reflux for 1 h, a solution of allyl bromide (10.5 mL, 120 mmol) in anhydrous THF (30 mL) was gradually added with a syringe pump within 2 h, keeping the reaction mixture under a gentle reflux. After the addition was complete, the mixture was stirred under reflux for an additional 30 min, and then the solvents were evaporated under reduced pressure ($T_{bath} < 70$ °C, 5 mbar). The residue was partitioned between diethyl ether (200 mL) and water (50 mL), the organic layer was separated, and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic phases were washed with water (50 mL), brine (100 mL) and dried over $MgSO_4$. The residue (12.6 g) obtained after evaporation of the solvents, was purified by flash chromatography on 100 mL of flash silica gel, eluting with pentane/ether, 5:1 to 2:1, to afford pure **7b**; yield: 8.2 g (55 %, based on allyl bromide), the physical constants and spectral data of which were identical to those reported in the literature.[10]

General Procedure for the Alkylation of 1,3-Dicarbonyl Compounds with 4-Chloro-2-butyn-1-ol (GP 1)

The respective 1,3-dicarbonyl compound **6e–i** (200 mmol) was added under nitrogen to a stirred suspension of LiOH (5.03 g, 210 mmol) and LiI (5.35 g, 40 mmol) in anhydrous THF (100 mL), and the resulting mixture was heated under reflux until it had become homogeneous (~30 min). After cooling to ambient temperature, 4-chloro-2-butyn-1-ol (23 g, 220 mmol) was added, and the mixture was stirred under reflux for 3 h. Then it was cooled to ambient temperature, poured into water (50 mL), and the mixture was extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with brine (100 mL), and the organic phase was dried over $MgSO_4$. The solvent was evaporated, and the residue was distilled under reduced pressure to afford the pure product. Non-volatile compounds were purified by first distilling off unreacted starting materials in a Kügelrohr (oven temperature < 140 °C), and then subjecting the residue to flash chromatography.

5-Acetyloct-7-en-2-yn-1-ol (7c)

After the alkylation of 3-allylpentane-2,4-dione (**6e**) (14.0 g, 100 mmol) according to GP 1 had been completed, a saturated solution of NaOH (4 g, 100 mmol) in anhydrous methanol was added dropwise to the reaction mixture with stirring under reflux within 1 h. Work-up as described above (GP 1) with subsequent distillation under reduced pressure afforded sufficiently pure **7c** as a pale-yellow liquid; yield: 13.5 g (81 %); bp 88–90 °C/0.1 mbar.

5-(Ethoxycarbonyl)oct-7-en-2-yn-1-ol (7d)

After the alkylation of ethyl 2-acetylpent-4-enoate (**6f**) (17.0 g, 100 mmol) according to GP 1 had been completed, a saturated solution of NaOH (4 g, 100 mmol) in anhydrous ethanol was added with stirring within 1 h to the reaction mixture kept under reflux. Work-up as described above (GP 1) with subsequent distillation under reduced pressure afforded sufficiently pure **7d** as a pale-yellow liquid; yield: 14.7 g (75 %): bp 87–90 °C/0.1 mbar.

5,5-Diacetyloct-7-en-2-yn-1-ol (7e)

Alkylation of 3-allylpentane-2,4-dione (**6e**) (16.8 g, 120 mmol) according to GP 1, after distillation under reduced pressure, gave pure **7e** as a colorless viscous oil; yield: 17.6 g (70 %); bp 120–130 °C/0.1 mbar.

5-Acetyl-5-(ethoxycarbonyl)oct-7-en-2-yn-1-ol (7f)

Alkylation of **6f** (34.2 g, 200 mmol) according to GP 1 gave 47.6 g of a crude product, which was subjected to fractional distillation under reduced pressure (0.002 mbar). The fraction boiling between 120 and 130 °C was collected to afford pure **7f** as a pale-yellow viscous oil, which showed no impurities in its ^{1}H NMR spectrum; yield: 38.1 g (80 %).

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5,5-Bis(ethoxycarbonyl)oct-7-en-2-yn-1-ol (7g)

To a stirred solution of diethyl allylmalonate (**6g**) (50.1 g, 250 mmol) and lithium iodide (6.69 g, 50 mmol) in anhydrous THF (250 mL) were added under nitrogen at ambient temperature DBU (41.9 g, 275 mmol) and then 4-chloro-2-butyn-1-ol (28.7 g, 275 mmol). The mixture was stirred at ambient temperature for 24 h, then it was poured into 5% aqueous sulfuric acid (100 mL) and the mixture was extracted with diethyl ether (3×200 mL). The combined organic layers were washed with brine (2×100 mL) and dried over $MgSO_4$. The solvents were evaporated under reduced pressure, and the residual brown oil (68 g) was distilled in a Kugelrohr to give two fractions: I: bp 80–130 °C/0.01–0.001 mbar, 7.1 g of starting materials contaminated with some by-products and II: bp 140 °C/0.001 mbar, 55.7 g (83% yield) of sufficiently pure **7g** as a pale-yellow viscous oil.

5-Benzoyl-5-(ethoxycarbonyl)oct-7-en-2-yn-1-ol (7h)

Alkylation of **6h** (22.4 g, 96 mmol) according to GP 1 after flash chromatography of the crude product (29 g) on flash silica gel (350 mL), eluting with hexane/ethyl acetate, 10:1 to 5:1, gave sufficiently pure **7h** as a pale-yellow viscous oil; yield: 18.4 g (64%).

5-(Ethoxycarbonyl)-5-(naphtho-2-yl)oct-7-en-2-yn-1-ol (7i)

To a mechanically stirred suspension of NaH (8.8 g of a 60% suspension in mineral oil, 220 mmol) in anhydrous THF (50 mL) was added diethyl carbonate (36.3 mL, 300 mmol), and the mixture was heated under reflux. Then, 10% of a solution of 2-acetylnaphthalene (17.1 g, 100 mmol) in THF (30 mL) was added all at once. After the reaction had started (hydrogen evolution), the heating bath was removed, and the remaining 90% of the solution was gradually added at such a rate as to keep the reaction mixture refluxing (*ca.* 1.5 h). After that, the mixture was heated until the hydrogen evolution had ceased (*ca.* 20 min), cooled, poured into 2 M H_2SO_4 (110 mL) and the mixture extracted with ether (3×100 mL). The combined extracts were washed with brine (100 mL) and dried over $MgSO_4$. The solvents were evaporated, and the residue (27.5 g) was added to a stirred suspension of $LiOH{\cdot}H_2O$ (4.19 g, 100 mmol) and LiI (2.68 g, 20 mmol) in anhydrous THF (50 mL) kept under reflux. After the mixture had become homogeneous (*ca.* 30 min), allyl bromide (10.5 mL, 120 mmol) was added, and heating under reflux was continued for 2 h. Then the mixture was cooled, diluted with water (30 mL) and extracted with ether (3×100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvents gave 31.3 g of crude **7i** (94% pure according to GC). This was added to a stirred suspension of anhydrous LiOH (2.39 g, 100 mmol) and LiI (2.68 g, 20 mmol) in anhydrous THF (50 mL), and the mixture was heated under reflux for 30 min. Then, 4-chlorobut-2-yn-1ol (9.05 mL, 105 mmol) was added, and the reaction mixture was kept under reflux for 4 h. After the renewed work-up, 38.8 g of crude product was obtained. For purification, the volatile by-products were removed by Kugelrohr distillation (130 °C/0.001 mbar), and the residue (28.1 g) was subjected to flash chromatography on 300 mL of silica gel eluting with hexane/ethyl acetate, 5:1 to 2:1, to afford pure **7i** as a pale-yellow viscous oil; yield: 16.1 g (46%).

General Procedure for *O*-Acylation of Propargyl Alcohols (GP 2)

To a stirred solution of the respective alcohol (100 mmol), NEt_3 (14.6 mL, 105 mmol) and DMAP (0.62 g, 5 mmol) in anhydrous CH_2Cl_2 (100 mL), chilled to −10 °C (ice/salt bath) under nitrogen, methyl chloroformate (11.0 g, 116 mmol) was added within 1 h keeping the temperature of the mixture under −5 °C. After stirring at this temperature for an additional 30 min, the cooling bath was removed, and most of the solvent was evaporated under reduced pressure at ambient temperature. The residue was then partitioned between water (50 mL) and diethyl ether (100 mL), the organic layer was separated and the aqueous one was extracted with ether (2×50 mL). The combined organic phases were dried over $MgSO_4$, the solvents were evaporated, the residual crude oil was distilled under reduced pressure or subjected to flash chromatography to give the respective pure product.

8-(Methoxycarbonyloxy)oct-1-en-6-yne (3a)

According to GP 2, alcohol **7a** (8.1 g, 65 mmol) after distillation of the crude product under reduced pressure, gave pure **3a** as a colorless liquid; yield: 11.1 g (94%); bp 60–62 °C/0.2 mbar.

8-(Methoxycarbonyloxy)-4-oxaoct-1-en-6-yne (3b)

According to GP 2, alcohol **7b** (11.4 g, 91 mmol) after distillation of the crude product under reduced pressure, gave pure **3b** as a colorless liquid; yield: 15.5 g (92%); bp 68–70 °C/0.1 mbar.

4-Acetyl-8-(methoxycarbonyloxy)oct-1-en-6-yne (3c)

According to GP 2, alcohol **7c** (9.97 g, 60 mmol) after distillation under reduced pressure, gave pure **3c** as a pale-yellow liquid; yield: 12.92 g (96%); bp 96–99 °C/0.1 mbar.

4-(Ethoxycarbonyl)-8-(methoxycarbonyloxy)oct-1-en-6-yne (3d)

According to GP 2, alcohol **7d** (18.5 g, 94 mmol) after distillation of the crude product (23.3 g) under reduced pressure, gave pure **3d** as a colorless liquid; yield: 22.3 g (93%); bp 103–105 °C/0.002 mbar.

4,4-Diacetyl-8-(methoxycarbonyloxy)oct-1-en-6-yne (3e)

According to GP 2, alcohol **7e** (14.6 g, 70 mmol) gave a crude product (18.4 g) as a pale-yellow oil, which was subjected to flash chromatography on 350 mL of silica gel, eluting with pentane/diethyl ether, 10:1 to 3:1, to afford pure **3e** as a colorless oil; yield: 16.9 g (91%).

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4-Acetyl-4-(ethoxycarbonyl)-8-(methoxycarbonyloxy) oct-1-en-6-yne (3f)

According to GP 2, alcohol **7f** (14.5 g, 61 mmol) gave a crude product (17.8 g) as a pale-yellow oil, which was subjected to flash chromatography on 350 mL of silica gel, eluting with pentane/diethyl ether, 10:1 to 3:1, to afford pure **3f** as a colorless oil; yield: 17.0 g (94%).

4,4-Bis(ethoxycarbonyl)-8-(methoxycarbonyloxy)oct-1-en-6-yne (3g)

According to GP 2, alcohol **7g** (13.4 g, 50 mmol) gave a crude product (16.5 g) as a pale-yellow oil, which was subjected to flash chromatography on 100 mL of silica gel, eluting with hexane/ethyl acetate, 10:1 to 5:1, to afford pure **3g** as a colorless oil; yield: 15.7 g (96%).

4-Benzoyl-4-(ethoxycarbonyl)-8-(methoxycarbonyloxy)oct-1-en-6-yne (3h)

According to GP 2, alcohol **7h** (14.9 g, 49.7 mmol) gave a crude product (17.8 g), which was subjected to flash chromatography on 250 mL of silica gel, eluting with hexane/ethyl acetate, 8:1 to 4:1, to afford pure **3h** as a pale-yellow oil; yield: 14.6 g (82%).

4-(Ethoxycarbonyl)-4-(naphtho-2-yl)-8-(methoxycarbonyloxy)oct-1-en-6-yne (3i)

According to GP 2, alcohol **7i** (15.6 g, 44.6 mmol) gave a crude product (17.5 g), which was subjected to flash chromatography on 250 mL of silica gel, eluting with hexane/ethyl acetate, 10:1 to 4:1, to afford pure **3i** as a pale-yellow oil; yield: 14.2 g (78%).

4-Benzoyl-8-(methoxycarbonyloxy)oct-1-en-6-yne (3j)

According to GP 1B, dibenzoylmethane **8** (11.2 g, 50 mmol), after flash chromatography on silica gel (100 mL), eluting with hexane/toluene/ethyl acetate, 5:5:2 to 5:5:4, gave sufficiently pure 6-hydroxy-1-phenylbut-4-yn-1-one (8.50 g, 90%) as a pale-yellow viscous oil. It was then subjected to GP 2 to give, after flash chromatography on 120 mL of silica gel, eluting with hexane/toluene/ethyl acetate, 5:5:1 to 5:5:2, the pure carbonate **9** (10.7 g, 96%) as a colorless viscous oil, which solidified in the refrigerator. The latter (10.7 g, 43.4 mmol) was dissolved in anhydrous THF (5 mL), and the solution added to a −78 °C cold solution of LiHMDS prepared from HMDS (10 mL, 47.7 mmol) and BuLi (18.2 mL of a 2.5 N solution in hexanes, 45.6 mmol) in THF (40 mL), keeping the internal temperature of the reaction mixture below −70 °C during the addition. The mixture was stirred at this temperature for an additional 1 h, and then *N,N*-dimethylpropyleneurea (DMPU) (6 mL, 50 mmol) and allyl bromide (5.7 mL, 66 mmol) were successively added at the same temperature. After 30 min, the cooling bath was removed, and the reaction mixture was stirred at ambient temperature for 16 h. Then it was poured into ice-cold 5% aqueous sulfuric acid (50 mL). The organic layer was separated, and the aqueous phase was extracted with ether (3× 50 mL). The combined organic phases were washed with 5% aqueous NaCl (2×50 mL), brine (100 mL) and dried over $MgSO_4$. The solvent was evaporated to give a brown viscous oil, which was subjected to flash chromatography on silica gel, eluting with hexane/toluene/ethyl acetate, 5:5:1 to 10:10:3, to afford pure **3j** as a colorless viscous oil; yield: 4.35 g (35%).

General Procedure for the Palladium-Catalyzed Bicyclization with Carbonylation of Enepropargyl Carbonates 3a–i (GP 3)

$Pd(OAc)_2$ (449 mg, 2 mmol) was added under argon to a solution of $P(2\text{-furyl})_3$ (1.02 g, 4.4 mmol), reducing agent (2.0–4.0 mmol) and dopand (2.2–80 mmol) in thoroughly degassed methanol (500 mL). After stirring at ambient temperature for 1 h, the respective enepropargyl carbonate **3a–i** (80 mmol) was added, the reaction atmosphere was replaced with CO (1 bar) provided in a rubber balloon, and the mixture was vigorously stirred at 25 °C, until the starting material had been completely consumed (*ca.* 24–48 h, GC or TLC control). Then the solvent was removed under reduced pressure to give a crude product, which was purified by flash or regular column chromatography on silica gel.

Methyl 2-(Bicyclo[3.1.0]hex-1-yl)propenoate (2a)

According to GP 3, the enyne **3a** (0.91 g, 5 mmol) was stirred for 16 h in the presence of $Pd(OAc)_2$ (2 mol%), TFP (4.4 mol%), $P(OMe)_3$ (4 mol%) and $OP(OMe)_3$ (10 mol%) to give, after flash chromatography on 20 mL of silica gel, eluting with pentane/ether, 20:1 to 15:1, pure **2a** as a colorless liquid; yield: 0.78 g (94%). The spectral data of the synthesized compound corresponded to those published previously.[5]

Methyl 2-(3-Oxabicyclo[3.1.0]hex-1-yl)propenoate (2b)

According to GP 3, the enyne **3b** (7.37 g, 40 mmol) was stirred for 48 h in the presence of $Pd(OAc)_2$ (2 mol%), TFP (4.4 mol%), $P(OMe)_3$ (4 mol%) and $OP(OMe)_3$ (10 mol%) to give, after flash chromatography on 80 mL of silica gel, eluting with pentane/ether, 10:1, pure **2b** as a colorless liquid; yield: 5.86 g (87%); bp 61–62 °C/2 mbar.

Methyl 2-(3-Acetylbicyclo[3.1.0]hex-1-yl)propenoate (2c)

According to GP 3, the enyne **3c** (450 mg, 2 mmol) was stirred for 24 h in the presence of $Pd(OAc)_2$ (2 mol%), TFP (4.4 mol%), $P(OMe)_3$ (4 mol%) and dibenzoylmethane (2 mol%) to give, after column chromatography on 50 mL of silica gel, eluting with hexane/*t*-BuOMe, 10:1, pure **2c** as a colorless liquid; yield: 266 mg (64%); 3:2 mixture of *endo*- and *exo*-diastereomers.

Methyl 2-[3-(Ethoxycarbonyl)bicyclo[3.1.0]hex-1-yl] propenoate (2d)

According to GP 3, the enyne **3d** (14.0 g, 55 mmol) was stirred for 48 h in the presence of $Pd(OAc)_2$ (2.5 mol%), TFP (5.5 mol%), $P(OMe)_3$ (5 mol%) and $OP(OMe)_3$ (5 mol%) to give, after column chromatography on 1 L of silica gel, eluting with hexane/*t*-BuOMe, 10:1, pure **2d** as a colorless

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liquid; yield: 9.11 g (69%); 1:1 mixture of *endo*- and *exo*-diastereomers.

Methyl 2-(3,3-Diacetylbicyclo[3.1.0]hex-1-yl)propenoate (2e)

According to GP 3, the enyne **3e** (15.50 g, 58 mmol) was stirred for 48 h in the presence of $Pd(OAc)_2$ (2 mol%), TFP (4.4 mol%), Me_4NBr (2.2 mol%) and toluene (100 mol%) to give, after column chromatography on 1 L of silica gel, eluting with hexane/*t*-BuOMe, 8:1, pure **2e** as a colorless oil; yield: 12.82 g (88%).

Methyl 2-[3-Acetyl-3-(ethoxycarbonyl)bicyclo[3.1.0]-hex-1-yl]propenoate (2f)

According to GP 3, the enyne **3f** (45.0 g, 152 mmol) was stirred for 48 h in the presence of $Pd(OAc)_2$ (2 mol%), TFP (4.4 mol%), Me_4NBr (2 mol%) and toluene (100 mol%) to give, after flash chromatography on 500 mL of silica gel, eluting with pentane/diethyl ether, 8:1 to 4:1, pure **2f** as a colorless oil; yield: 38.8 g (91%); 2:1 mixture of *endo*- and *exo*-diastereomers.

Methyl 2-[3,3-Bis(ethoxycarbonyl)bicyclo[3.1.0]hex-1-yl]propenoate (2g)

According to GP 3, the enyne **3g** (7.37 g, 22.6 mmol) was stirred for 24 h in the presence of $Pd(OAc)_2$ (2.5 mol%), TFP (5.5 mol%), Me_4NBr (2.7 mol%) and toluene (100 mol%) to give, after flash chromatography on 100 mL of flash silica gel, eluting with pentane/diethyl ether, 10:1 to 5:1, pure **2g** as a colorless oil; yield: 6.03 g (86%).

Methyl 2-[3-Benzoyl-3-(ethoxycarbonyl)bicyclo[3.1.0]hex-1-yl]propenoate (2h)

According to GP 3, the enyne **3h** (15.2 g, 42 mmol) was stirred for 60 h in the presence of $Pd(OAc)_2$ (3 mol%), TFP (6.6 mol%), Me_4NBr (3.3 mol%) and toluene (100 mol%) to give after column chromatography on 1 L of silica gel, eluting with hexane/ethyl acetate, 8:1, pure **2h** as a pale-yellow viscous oil; yield: 12.1 g (84%); mixture of *endo*- and *exo*- diastereomers.

Methyl 2-[3-(Ethoxycarbonyl)-3-(naphtho-2-yl)-bicyclo[3.1.0]hex-1-yl]propenoate (2i)

According to GP 3, the enyne **3i** (14.2 g, 34.8 mmol) was stirred for 24 h in the presence of $Pd(OAc)_2$ (3 mol%), TFP (6.6 mol%), Me_4NBr (3.3 mol%) and BHT (3.3 mol%) to give, after flash chromatography on 350 mL of silica gel, eluting with hexane/ethyl acetate, 10:1 to 8:1, pure **2i** as a pale-yellow viscous oil; yield: 11.9 g (87%); 1:1 mixture of *endo*- and *exo*- diastereomers.

Methyl 2-(3-Benzoylbicyclo[3.1.0]hex-1-yl)propenoate (2j)

According to GP 3, the enyne **3j** (477 mg, 1.67 mmol) was stirred for 24 h in the presence of $Pd(OAc)_2$ (3 mol%), TFP (6.6 mol%), $P(OMe)_3$ (6 mol%) and camphor (3.3 mol%) to give, after column chromatography on 80 mL of silica gel, eluting with hexane/*t*-BuOMe, 20:1, pure **2j** as a colorless viscous oil; yield: 270 mg (60%); 7:3 mixture of *endo*- and *exo*-diastereomers, an aliquot of which was separated to afford an analytical sample of each diastereomer.

General Procedure for the Palladium-Catalyzed Carbonylation of Enepropargyl Carbonates 3a–c under Increased Pressure (GP 4)

A reaction vessel for reactions under increased pressure was charged with enyne **3a–c** (2.50 mmol), TFP (38.3 mg, 0.165 mmol, 6.6 mol%), Me_4NBr (12.7 mg, 0.082 mmol, 3.3 mol%), BHT (16.5 mg, 0.075 mmol, 3 mol%) and methanol (25 mL), and stoppered with a three-way stopcock connected with a vacuum pump and an argon line. The mixture was stirred until it became homogenous and then chilled to −78 °C. After three freeze/pump cycles, the stopcock was removed, $Pd(OAc)_2$ (16.8 mg, 0.075 mmol, 3 mol%) was added quickly at −78 °C, and the vessel was in turn connected with a high-pressure line. Then the system was immediately evacuated, and CO was introduced until a pressure of 5 bar had been reached. The mixture was warmed up to ambient temperature and stirred under constant pressure for the required time (12–24 h). The residue obtained after evaporation of the solvent, was subjected to column chromatography.

Methyl 2-Vinylidenehept-6-enoate (10a)

According to GP 4, the enyne **3a** (455 mg, 2.50 mmol) was stirred for 12 h to give, after flash chromatography on 20 mL of silica gel, eluting with pentane/ether, 20:1 to 10:1, 395 mg of a 2:1 mixture of **10a** and **2a** (according to GC) contaminated with *ca.* 20% of unidentified by-products. An aliquot of this was subjected to column chromatography on 80 mL of silica gel (eluent pentane/diethyl ether, 20:1) to afford an analytically pure sample of **10a**.

Methyl 4-Oxa-2-vinylidenehept-6-enoate (10b)

According to GP 4, the enyne **3b** (460 mg, 2.50 mmol) was stirred with the catalyst for 16 h to give, after column chromatography, 310 mg (74%) of an inseparable 55:45 mixture of **2b** and **10b**.

Methyl 4-Acetyl-2-vinylidenehept-6-enoate (10c)

According to GP 4, the enyne **3c** (561 mg, 2.50 mmol) was stirred with the catalyst for 12 h to give, after flash chromatography on 20 mL of silica gel, eluting with pentane/ether, 20:1 to 10:1, 393 mg of a mixture of approximately equal amounts of **2c**, **3c** and **10c** (according to GC). An aliquot of this was subjected to column chromatography on 80 mL of silica gel (eluent pentane/diethyl ether, 20:1) to afford an inseparable 1:2 mixture of ***endo*-2c** and **10c**.

Methyl 4-(Ethoxycarbonyl)-2-vinylidenehept-6-enoate (10d)

According to GP 3, the enyne **3d** (635 mg, 2.50 mmol) was stirred with the catalyst for 16 h in the presence of 2 mol% of catalyst B to give, after flash chromatography on 20 mL

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of silica gel, 410 mg of 3:1 mixture of **2d** and **10d** also containing unidentified contaminations. An aliquot of this was subjected to column chromatography on 80 mL of silica gel (eluent pentane/diethyl ether, 20:1) to afford an analytically pure sample of **10d**.

General Procedure for the Hydrolysis of Bicyclic Methyl Acrylates[33] (GP 5)

To a well stirred solution of the respective bicyclic acrylate (80 mmol) and BHT (10 mg) in acetone/water, 8:1 (180 mL) was added under nitrogen a 4 N aqueous solution of lithium hydroxide (40 mL, 160 mmol). The mixture was stirred at ambient temperature until the starting material had been consumed (*ca.* 24 h, TLC control). Then, the solvents were removed under reduced pressure at ambient temperature, and the residue was dissolved in a minimal amount of water. The aqueous phase was washed with ether (2×50 mL), acidified with 12 N HCl (13.5 mL) and the mixture extracted with ether (4×50 mL). The combined organic layers were washed with brine (2×50 mL) and dried over Na_2SO_4. Evaporation of the solvent left the sufficiently pure target bicyclo[3.1.0]hexylacrylic acid (according to NMR data), which was used for esterifications in the next step without any additional purification.

2-(Bicyclo[3.1.0]hex-1-yl)propenoic Acid (12a)

Hydrolysis of **2a** (13.3 g, 80 mmol) according to GP 5 gave **12a** (pure according to its NMR data) as a colorless crystalline material, which had a tendency to polymerize rapidly when exposed to air and without a stabilizer added (BHT); yield: 10.5 g (86%); mp 60.5–61.0 °C.

Methyl 2-(3-Oxabicyclo[3.1.0]hex-1-yl)propenoic Acid (12b)

According to GP 5, crude **2b** (0.60 g, 85% according to GC) gave after recrystallization of the crude reaction mixture from toluene/cyclohexane, 4:1, pure **12b** as colorless crystals; yield: 0.35 g (80%); mp 86.5–87.0 °C.

Direct Synthesis of 2-[3,3-Bis(ethoxycarbonyl) bicyclo[3.1.0]hex-1-yl]propenoic Acid (12g) by Palladium-Catalyzed Bicyclization-Carboxylation of the 1,6-Enyne 3g

To a stirred solution of P(2-furyl)$_3$ (766 mg, 3.30 mmol), Me_4NBr (254 mg, 1.65 mmol), BHT (397 mg, 1.80 mmol) and the enyne **3g** (16.3 g, 50 mmol) in degassed 60% aqueous AcOH (1000 mL), was added under argon $Pd(OAc)_2$ (337 mg, 1.50 mmol), and the mixture was stirred at 25 °C for 1 h. Then, the reaction atmosphere was replaced with CO (provided in a rubber balloon), and the mixture was vigorously stirred at ambient temperature until the starting 1,6-enyne **3g** had been completely consumed (*ca.* 24 h, TLC control). The solvents were removed under reduced pressure (T_{bath} = 40 °C/0.5 mbar), the residue was suspended in diethyl ether (200 mL), and the mixture was filtered through Celite. The product was extracted with 0.2 M aqueous Na_2CO_3 (250 mL), the aqueous extract was washed with ether (2×50 mL), then ether (100 mL) and BHT (10 mg) were added, and the aqueous phase was acidified with 12 N HCl (*ca.* 4–5 mL) to pH 1. The organic layer was separated, and the aqueous one was saturated with NaCl and re-extracted with ether (3×50 mL). The combined organic phases were washed with brine (100 mL) and dried over Na_2SO_4. The solvent was evaporated to afford 10.8 g (73%) of the pure acid **12g** as a pale-yellow viscous oil, which was immediately used for esterifications without additional purification.

General Procedure for the Esterification of Bicyclo[3.1.0]hexylacrylic Acids (GP 6)

To a stirred solution of the respective bicyclo[3.1.0]acrylic acid (50 mmol), the respective alcohol (50 mmol) and triphenylphosphine (13.4 g, 51 mmol) in anhydrous THF (100 mL), kept at −78 °C (dry ice/acetone bath) under nitrogen, was gradually added diethyl azodicarboxylate (8.88 g, 51 mmol), while the temperature of the mixture was kept at or below −70 °C. After stirring for an additional 30 min, the cooling bath was removed, the reaction mixture was allowed to reach room temperature, and the solvent was evaporated under reduced pressure at ambient temperature. The residue was suspended by stirring with *t*-BuOMe (~30 mL) and diluted by gradual addition of pentane (150 mL). After stirring with cooling (ice-water bath) for an additional 1 h, the suspension was filtered through a short plug of flash silica gel (∅ 65×30 mm) and washed with pentane/*t*-BuOMe, 5:1 (2×50 mL). The solvents were removed from the combined filtrates to afford a crude product, which was finally purified by regular column or flash chromatography.

1,6-Bis[2-(bicyclo[3.1.0]hex-1-yl)propenoyloxy]hexane (13a)

According to GP 6, the acid **12a** (11.0 g, 72.2 mmol) and 1,6-hexanediol (4.27 g, 36.1 mmol) gave 13.7 g of the crude diester **13a**, which was purified by column chromatography on 1 L of silica gel (column ∅ 70 mm), eluting with hexane/*t*-BuOMe, 20:1, to afford pure **13a** as a colorless viscous oil; yield: 11.7 g (84%).

1,6-Bis{2-[3,3-bis(ethoxycarbonyl)bicyclo[3.1.0]hex-1-yl]propenoyloxy}hexane (13g)

According to GP 6, the acid **12g** (12.0 g, 40.5 mmol) and 1,6-hexanediol (2.39 g, 20.2 mmol) afforded, after flash chromatography on 300 mL of silica gel (column ∅ 100 mm), eluting with hexane/ethyl acetate, 6:1 to 4:1, the pure diester **13g** as a colorless viscous oil; yield: 11.7 g (86%).

2-(Bicyclo[3.1.0]hex-1-yl)propenoyl Chloride (14a)

To a stirred solution of the acid **12a** (3.04 g, 20 mmol), BHT (2 mg, 0.01 mmol) and a few drops of DMF (*ca.* 0.05 mL) in anhydrous CH_2Cl_2 (10 mL) was added oxalyl chloride (2.1 mL, 25 mmol) under argon at ambient temperature. The mixture was stirred at this temperature, until the gas evolution had ceased (*ca.* 3 h), then the solvent was evaporated under reduced pressure (about 10 mbar) at ambient temperature. The evaporation was terminated as soon as the temperature of the reaction mixture had reached 20 °C. The crude mixture was dissolved in anhydrous CCl_4 (20 mL) and evaporated under reduced pressure by the same way, and the residue was bulb-to-bulb distilled (T_{bath} < 60 °C, 0.5 Torr)

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to afford sufficiently pure **14a**; yield: 3.17 g (93%). An analytically pure sample was obtained by distillation of an aliquot of the crude reaction mixture under reduced pressure, bp 63–64 °C/4 mbar.

Benzyl 2-(Bicyclo[3.1.0]hex-1-yl)propenoate (15a)

To a stirred suspension of finely powdered and flame-dried K_2CO_3 (5 g, 36.2 mmol) and KI (3.8 g, 22.9 mmol) in anhydrous DMF (40 mL) was added under argon a solution of the acid **12a** (3.3 g, 21.7 mmol) and benzyl chloride (2.9 g, 22.9 mmol) in 10 mL of the same solvent in one portion at ambient temperature. After stirring for an additional 12 h, the mixture was poured into 250 mL of *t*-BuOMe and filtered through a short pad of Celite®, which was rinsed with 50 mL of the same solvent. The filtrate was washed with water (2×150 mL), brine (100 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvents under reduced pressure gave 5.2 g of a crude product, which was subjected to flash chromatography on 100 mL of silica gel, eluting with pentane to pentane/ether, 20:1, to afford pure **15a** (99.8% pure according to GC); yield: 4.75 g (90%).

Adamant-1-yl 2-(Bicyclo[3.1.0]hex-1-yl)propenoate (16a)

To a stirred solution of the respective alcohol (3.03 g, 20 mmol), anhydrous triethylamine (25 mmol) and DMAP (488 mg, 4.0 mmol, 20 mol%) in anhydrous CH_2Cl_2 (35 mL), kept at −5 °C (ice/salt bath) under nitrogen, was added a solution of the acid chloride **14a** (3.41 g, 20 mmol) in the same solvent (5 mL) at such a rate that the temperature of the reaction mixture did not exceed 0 °C (10–30 min). Then the cooling bath was removed, and the mixture was stirred at ambient temperature for an additional 36 h. After that, most of the solvent was evaporated under reduced pressure at ambient temperature, and the residue was suspended with stirring in pentane (*ca.* 80 mL) and the mixture filtered through a short pad of flash silica gel (*ca.* 20 mL). The silica gel was rinsed with pentane/ether, 10:1 mixture (40 mL), and the combined filtrates were evaporated under reduced pressure to give 5.85 g of crude **16a**, which was purified by column chromatography on 500 mL of silica gel, eluting with hexane/*t*-BuOMe, 40:1, to afford pure **16a** (>99% pure according to GC) as a viscous colorless oil; yield: 4.35 g (76%). Low-temperature recrystallization of the aliquot from methanol/acetone, 2:1, afforded an analytically pure sample of **16a** as a white powder; mp 41–42 °C.

(1*R/S,2′S*)-*endo*-1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl 2-(Bicyclo[3.1.0]hex-1-yl)propenoate (17a)

Alcoholysis of the acid chloride **14a** (3.41 g, 20 mmol) with (1*S*)-*endo*-(−)-borneol (3.08 g, 20 mmol) in the presence of 110 mol% of DMAP (2.69 g, 22 mmol) was performed as above (see synthesis of **16a**, the reaction mixture was stirred at ambient temperature for 48 h) and gave 4.0 g of crude **17a**, which was purified by column chromatography on 500 mL of silica gel, eluting with hexane/toluene, 6:1, to afford pure **17a** (>98% pure according to GC) as a viscous colorless oil; yield: 3.6 g (63%).

Supporting Information

Full characterization data for all new compounds, and ^{1}H- and ^{13}C NMR spectra for **7i**, **2j**, **10a**, and **10d**.

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References

[1] Part 130: F. Brackmann, N. Colombo, C. Cabrele, A. de Meijere, *Eur. J. Org. Chem.* **2006**, 4440–4450. Part 129: I. Nakamura, T. Nemoto, Y. Yamamoto, A. de Meijere, *Angew. Chem.* **2006**, *118*, 5300–5303; *Angew. Chem. Int. Ed.* **2006**, *45*, 5176–5179.
[2] C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813–834.
[3] A. Fürstner, H. Szillat, B. Gabor, R. Mynott, *J. Am. Chem. Soc.* **1998**, *120*, 8305–8314.
[4] A. de Meijere, V. Bagutski, F. Zeuner, U. K. Fischer, V. Rheinberger, N. Moszner, *Eur. J. Org. Chem.* **2004**, 3669–3678.
[5] N. Moszner, F. Zeuner, U. K. Fischer, V. Rheinberger, A. de Meijere, V. Bagutski, *Macromol. Rapid Commun.* **2003**, *24*, 269–273.
[6] N. Moszner, F. Zeuner, V. Rheinberger, U. K. Fischer, A. de Meijere, (Ivoclar Vivadent AG), *German Patent* 10,249,324, **2002**.
[7] R. Grigg, R. Rasul, J. Redpath, D. Wilson, *Tetrahedron Lett.* **1996**, *37*, 4609–4612.
[8] W. Oppolzer, A. Pimm, B. Stammen, W. E. Hume, *Helv. Chim. Acta* **1997**, *80*, 623–639.
[9] P. C. B. Page, C. M. Rayner, I. O. Sutherland, *J. Chem. Soc., Perkin Trans. 1* **1990**, 1375–1382.
[10] R. J. Fletcher, C. Lampard, J. A. Murphy, N. Lewis, *J. Chem. Soc., Perkin Trans. 1* **1995**, 623–633.
[11] The target 2-(bicyclo[3.1.0]hex-1-yl)acrylates produced for an ultimate use in low-shrinkage dental composites, must remain colorless even after extended exposure to air and light. They also should have minimal biological activity, e.g. cytotoxity.
[12] A. G. Steinig, A. de Meijere, *Eur. J. Org. Chem.* **1999**, 1333–1344.
[13] W. J. Bailey, E. Fujiwara, *J. Am. Chem. Soc.* **1955**, *77*, 165–166. The original protocol was modified (see Experimental Section).
[14] R. Antonioletti, F. Bonadies, L. R. Orelli, A. Scettri, *Gazz. Chim. Ital.* **1992**, 237–238.
[15] With this modification even less C–H acidic α-acetylamides can be alkylated.
[16] H. Oediger, F. Möller, *Liebigs. Ann. Chem.* **1976**, 348–351.

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[17] Palladium acetate has been applied as a precatalyst for carbonylative transformations of propargyl carbonates. J. Tsuji, T. Mandai, *Angew. Chem.* **1995**, *107*, 2830–2854; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2589–2612.
[18] Use of at least two equivalents of $P(2\text{-fur})_3$ with respect to $Pd(OAc)_2$ is essential. All attempts to perform the bicyclization either under ligand-free conditions, or in the presence of less ligand either failed completely or led to immediate formation of palladium black.
[19] Trialkyl phosphites are known to be able to reduce palladium(II) to palladium(0), see: I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066.
[20] The favorable role of the quaternary ammonium halide most probably is to provide an appropriate concentration of halide ions which help to stabilize the palladium(0) species, see: C. Amatore, A. Jutand, *Acc. Chem. Res.* **2000**, *33*, 314–321.
[21] It is noteworthy, that the use of a tetraalkylammonium iodide causes immediate formation of palladium black.
[22] For the influence of *gem*-disubstitution on the success of cyclization reactions see the review: M. E. Jung, G. Piizzi, *Chem. Rev.* **2005**, *105*, 1735–1766.
[23] J. Tsuji, T. Sugiura, I. Minami, *Tetrahedron Lett.* **1986**, *27*, 731–734.
[24] S. Winstein, E. C. Friedrich, R. Baker, Y. Lin, *Tetrahedron* **1966**, *Suppl. 8*, *Part II*, 621–645.
[25] D. S. Yufit, V. Bagutski, J. A. K. Howard, A. de Meijere, *Acta Crystallogr.* **2003**, *E59*, o1610–o1612.
[26] V. Bagutski, *Dissertation*, Universität Göttingen, **2004**, p. 145.
[27] An attempted bicyclization of **7g** in glacial acetic acid gave only a trace amount (*ca.* 5%) of the corresponding bicyclic acrylic acid.
[28] N. Moszner, F. Zeuner, U. K. Fischer, V. Rheinberger, A. de Meijere, V. Bagutski, *Macromol. Mater. Eng.* **2006**, *291*, 83–89.
[29] L. M. Harwood, *Aldrichimica Acta* **1985**, *18*, 25.
[30] J. Cervelló, J. Marquet, M. Moreno-Mañas, *Synth. Commun.* **1990**, *20*, 1931–1941.
[31] J. M. Mellor, S. Mohammed, *Tetrahedron* **1993**, *49*, 7567–7578.
[32] R. Queignec, B. Kirschleger, F. Lambert, M. Aboutaj, *Synth. Commun.* **1988**, *18*, 1213–1223.
[33] This procedure is also viable for the hydrolysis of ethyl acrylates to give the corresponding acids in excellent yields: V. Bagutski, *Dissertation*, Universität Göttingen, **2004**, p. 77.

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