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O-Methoxycarbonyl Cyanohydrin as a New Protective Group for Carbonyls

David Berthiaume and Donald Poirier*

Medicinal Chemistry Division, Oncology and Molecular Endocrinology Research Center, Laval University Medical Center (CHUL), 2705 Laurier Boulevard, Quebec G1V 4G2, Canada

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Abstract—*O*-Methoxycarbonyl cyanohydrin, a new protective group of carbonyls, was prepared in high yields by an efficient one-step procedure using methyl cyanoformate and a secondary alkylamine at room temperature. Herein, we report efficient methods for the formation and cleavage of the protective group. Also, the ability of different types of carbonyls to be protected and the protective group's behavior under different chemical conditions were studied.

Introduction

The protection and deprotection of carbonyl groups are common and necessary processes in organic synthesis, so a large variety of protective groups have been developed for this purpose.[1] Among them, the *O*-substituted cyanohydrin family counts four derivatives: acetyl,[2,3] silyl,[4–7] ethoxyethyl,[8] and tetrahydropyranyl.[9] During the course of our studies on the synthesis of C18-steroid derivatives as inhibitors of 17β-hydroxysteroid dehydrogenase and steroid sulfatase,[10–17] we found that *O*-methoxycarbonyl cyanohydrin **2** can be easily obtained from a C17-steroid ketone **1** by a one-step procedure (Scheme 1).

To date, synthesis of *O*-methoxycarbonyl cyanohydrins has been reported in moderate yields for aldehydes and aromatic ketones solely.[18–20] This fact led us to optimize the reactive conditions of this one-step formation of **2**. A preliminary account of this unexpected formation of substituted cyanohydrins from ketones has recently been reported by our group.[21] We now report a full account of the formation and cleavage of the *O*-methoxycarbonyl cyanohydrin group on carbonyls and the characteristics of this new protective group.

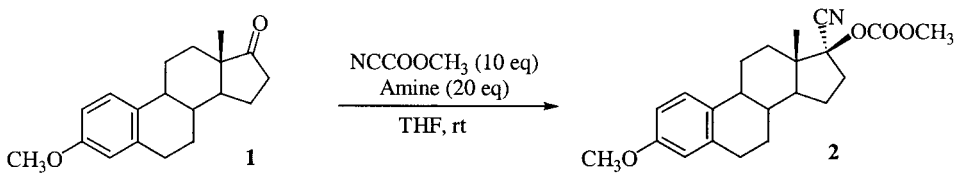
Protective Group Formation

Equivalents of amine needed

The steroid ketone **1** was selected for the first part of our study. We started by determining the number of diisopropylamine (DIPA) equivalents that were necessary to produce the desired cyanohydrin carbonate **2** (Table 1). The conditions used were 10 equiv. of methyl cyanoformate in THF at room temperature. We noted that the presence of amine was crucial as the reaction did not take place without DIPA (entry 1). Yields and reaction rates increased with the addition of DIPA from 0 to 20 equiv. (entries 1–4), but at 50 equiv. yields dropped (entry 5). We kept 20 equiv. of DIPA as a standard condition for the next tests.

Effect of water, air and temperature on the reaction

We tested whether the presence of water or air could be interfering with the reaction (Table 2). As illustrated, the addition of one drop of water completely blocked the reaction (entry 6). The reaction proceeded under both argon and air atmospheres with no significant differences (entries 7 and 8). Since ambient air humidity did not



Scheme 1. Protective group formation.

Keywords: protecting groups; aldehydes; ketones; cyanohydrins; carbonates.
* Corresponding author. Tel.: +1-418-654-2296; fax: +1-418-654-2761; e-mail: donald.poirier@crchul.ulaval.ca

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Table 1. Formation of derivative **2** from steroid ketone **1**: effect of reaction time and diisopropylamine (DIPA) equivalents

Entry	DIPA (equiv.)	Yields (%)[a]			
		4 h	8 h	12 h	24 h
1	0	0	0	0	0
2	5	18	54	75	86
3	10	21	52	75	95
4	20	31	67	85	91
5	50	61	72	77	75

[a] Yields were determined by ^{1}H NMR.

Table 2. Formation of derivative **2** from steroid ketone **1**: effect of water presence

Entry	Conditions[a]	Yields (%)[b]		
		4 h	24 h	48 h
6	a	0	0	0
7	b	44	92	91
8	c	43	96	96

[a] Conditions: (a) air atmosphere+water drop; (b) dry THF and argon atmosphere; (c) air atmosphere.
[b] Yields were determined by ^{1}H NMR.

Table 3. Formation of derivative **2** from steroid ketone **1**: effect of temperature

Entry	Temperature (°C)	Yields (%)[a]		
		4 h	8 h	24 h
9	−78	0	2	–
10	0	35	65	–
11	20	31	67	91
12	65	70	70	71

[a] Yields were determined by ^{1}H NMR.

interfere with the reactions, all other experiments were performed in air. The way the reaction behaved under different temperatures was then studied (Table 3). The protective group was not obtained at −78°C (entry 9). At 65°C, the reaction rate accelerated and we rapidly obtained 70% yields after just 4 h, but the reaction did not run to completion (entry 12). The yields obtained at 0 and 20°C (entries 10 and 11) were the same so the next experiments were performed at room temperature. We also repeated this experiment on a conjugated ketone (17β-(*t*-butyldimethylsilyl)testosterone) keeping the same temperatures to see if it had an effect on the reactivity of conjugated ketones. The effect of the temperature on the reaction was the same as on the unconjugated ketones and did not give better yields than at room temperature. The fact that a higher temperature accelerates the reaction but causes the maximum yields to drop indicates that an equilibrium is probably involved in the reaction mechanism. At low temperatures, equilibrium would enable a near quantitative yield of the desired cyanohydrin derivative, but at high temperature, the equilibrium would shift a bit toward the ketone substrate.

Table 4. Formation of derivative **2** from steroid ketone **1**: effect of solvent

Entry	Solvent	Yields (%)[a]			
		2 h	4 h	8 h	24 h
13	DMF	40	55	61	61
14	MeCN	23	38	67	71
15	EtOAc	8	25	66	97
16	THF	15	38	77	95
17	CH_2Cl_2	25	34	49	73
18	Toluene	42	60	72	83

[a] Yields were determined by ^{1}H NMR.

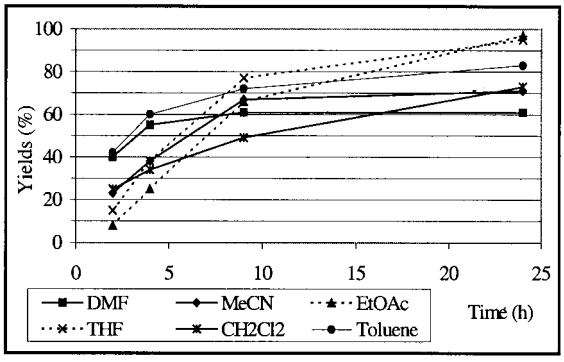


Figure 1. Yields obtained for the formation of derivative **2** from steroid ketone **1** with different solvents in function of reaction time.

Effect of the solvent on the reaction

We tried experimenting with different solvents (Table 4 and Fig. 1) and used dimethylformamide (DMF), acetonitrile (MeCN), ethyl acetate (EtOAc), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and toluene. Both EtOAc and THF gave higher than 95% yields (entries 15 and 16). Surprisingly, solvents that were slow to start the reaction gave better yields than fast start solvents; so apparently two steps are involved in the formation of the cyanohydrin derivative. Our hypothesis is that solvent favoring the first step would impede the second one, thus preventing its completion. On the other hand, solvent favoring the second step would make the first step more difficult, explaining the

Table 5. Formation of derivative **2** from steroid ketone **1** in THF: effect of different amines

Entry	Amine	Yields (%)[a]			
		2 h	4 h	8 h	24 h
19	*N*-Butylamine	–	0	0	0
20	Diphenylamine	–	–	0	–
21	Diallylamine	–	–	0	–
22	Dipropylamine	–	0	0	0
23	Pyrrolidine	0	0	0	0
24	*N*-Ethylisopropylamine	0	3	6	10
25	Triethylamine[b]	4	24	36	44
26	Dimethylaminopyridine[b]	30	48	58	56
27	Diisopropylamine	8	22	58	96
28	*N*-Isopropylcyclohexylamine	9	23	60	95
29	2,2,6,6-Tetramethylpiperidine	22	43	70	92
30	*N*-*t*-Butylethylamine	45	70	96	93
31	*cis*-2,6-Dimethylpiperidine	31	71	96	99

[a] Yields were determined by ^{1}H NMR.
[b] Yellow tar formed instead of dark red solution.

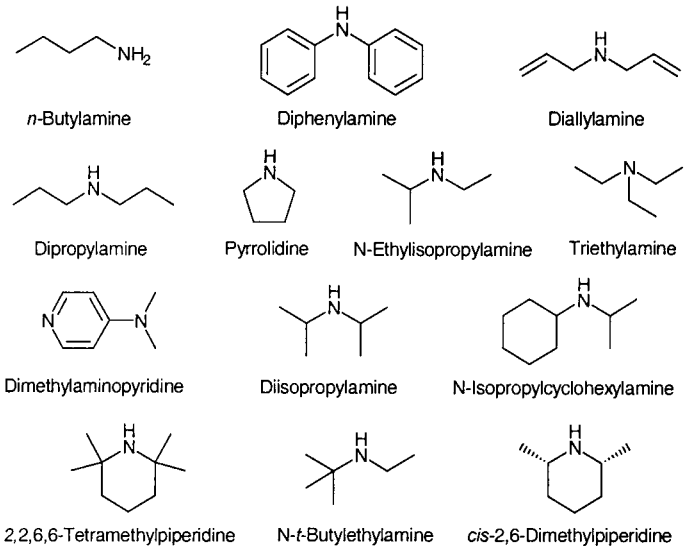


Figure 2. Structures of the amines used.

slow start in these cases. We kept THF as solvent for our next experiments but EtOAc is also a good solvent for the reaction.

Effect of the type of the amine

We tried to determine the most appropriate amine by doing the reaction with a wide range of different amines (Table 5 and Figs. 2 and 3). Clearly, a primary amine (entry 19) is not suitable to perform the protection. The type of amine was also important since no protection occurred with diphenylamine and diallylamine (entries 20 and 21). In the dialkylamine series, dipropylamine and pyrrolidine were not better with no protective group detected (entries 22 and 23). *N*-Ethylisopropylamine gave some protected ketone in 10% yields (entry 24). Reactions with triethylamine and dimethylaminopyridine produced some protective group but the yields obtained never went above 44 and 58%, respectively (entries 25 and 26). In these two cases, yellow tar appeared in the flask instead of the red color solution like other effective amines. Better results were obtained with diisopropylamine, *N*-isopropylcyclohexylamine and 2,2,6,6-tetramethylpiperidine with 96, 95 and 92% yields of **2** respectively (entries 27–29). These yields were obtained after 24 h of reaction though. Even better results were obtained with *N*-*t*-butylethylamine and *cis*-2,6-dimethylpiperidine with yields of 96% in only 8 h (entries 30 and 31). It seems that only very hindered and ramified secondary amines are able to produce the wanted reaction in good yields. For the sake of uniformity, low cost and because yields obtained were good, we kept diisopropylamine in our next experiments.

Concentration and equivalents of methyl cyanoformate needed

We attempted the reaction using DIPA as the only solvent but the substrates were not soluble in neat amine, so we repeated the reaction with a mixture of DIPA/THF (1:1) instead. The quantity of the solvent mixture used to dissolve the ketone substrate was calculated to get the required 20 equiv. of amine. In these conditions, we were able to

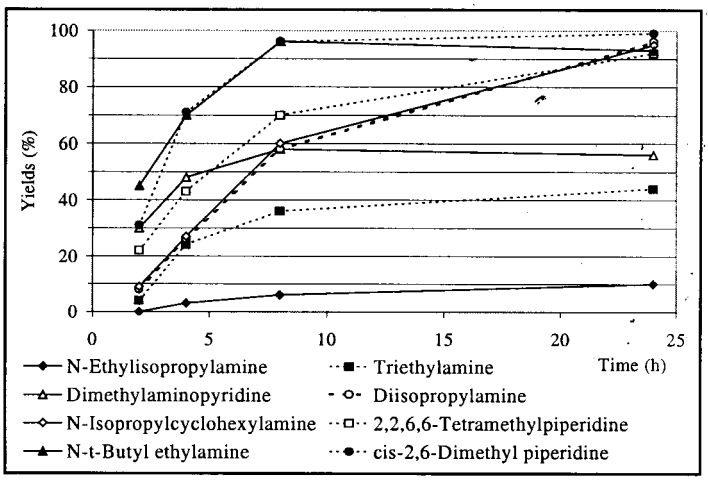
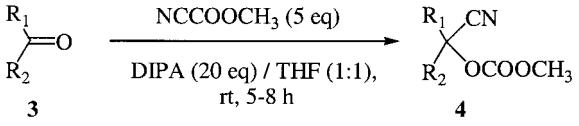


Figure 3. Yields obtained for the formation of derivative **2** from steroid ketone **1** in THF with different amines versus reaction time.

Table 6. Formation of derivative **2** from steroid ketone **1** in THF: effect of reaction time and methyl cyanoformate (MCF) equivalents

Entry	MCF (equiv.)	Yields (%)[a]				
		1 h	2 h	3 h	4 h	5 h
32	1	0	1	1	2	1
33	2	7	13	25	33	39
34	5	31	36	65	80	92
35	10	20	61	83	89	93

[a] Yields were determined by ^{1}H NMR.



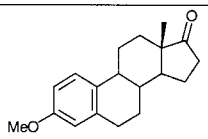
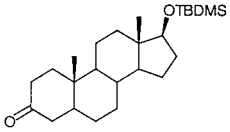
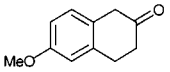
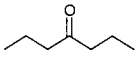
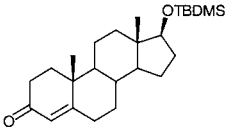
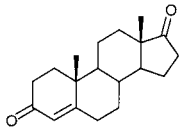
Scheme 2. Standard conditions for the formation of *O*-methoxycarbonyl cyanohydrins **4** from carbonyls **3**.

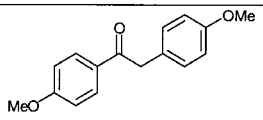
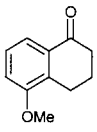
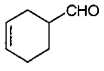
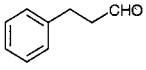
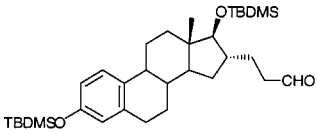
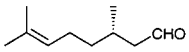
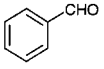
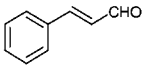
obtain the cyanohydrin carbonate in 93% yield in only 5 h (Table 6, entry 35). Having achieved the formation of the protecting group in a short time, we tried to reduce the number of equivalents of methyl cyanoformate to 1 or 2 equiv., but this was not enough to give good yields (entries 32 and 33). At 5 and 10 equiv., comparable yields resulted after 5 h (entries 34 and 35), so 5 equiv. of methyl cyanoformate was retained as a standard condition for the formation of the protecting group.

Carbonyls Reactivity

The ability of a series of different types of carbonyl groups to be protected was also studied, and we determined the isolated yields (Scheme 2 and Table 7). Diisopropylamine (DIPA) was selected for these assays. Two different conditions are reported: those for the first experiments (1.00 mmol of substrate, 10 equiv. of methyl cyanoformate

Table 7. Formation of *O*-methoxycarbonyl cyanohydrin derivatives **4** from carbonyl substrates **3**

Entry	Substrate **3**	Cond.[a]	Yield (%)[b]
36		a	92
		b	92
37		a	93
		b	93
38		b	85
39		a	94
		b	95
40		a	50
		b	57
41		a	18
		b	25
42		a	28
43[c]		a	*a* : 60 *b* : 28 *c* : 9

Entry	Substrate **3**	Cond.[a]	Yield (%)[b]
44		b	19
45		a	15
		b	15
46		a	95
47		a	92
48		a	72[d]
49		a	84
50		a	64
51		a	-[e]

[a] Conditions: (a) 1.00 mmol of **3** and 5 equiv. of methyl cyanoformate in a DIPA (20 equiv.)/THF (1:1) mixture for 5–8 h. (b) 1 mmol of **3**, 10 equiv. of methyl cyanoformate and 20 equiv. of DIPA in 5 mL of THF for 24 h.
[b] Isolated yields after chromatography.
[c] Yields for each product: *a* (C-17 protected), *b* and *c* (two C-3 isomers of C-17 and C-3 diprotected).
[d] For 0.60 mmol of substrate.
[e] The protective group was not observed, we rather isolated the product of a double bond reduction.

and 20 equiv. of DIPA in 5 mL of THF, 24 h), and others used for the last ones (1.00 mmol of substrate and 5 equiv. of methyl cyanoformate in a DIPA (20 equiv.)/THF (1:1) mixture, 5–8 h). The yields obtained with these two conditions are very similar. The only difference was the reaction time.

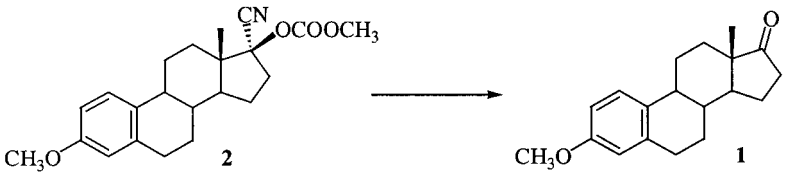
Under standard conditions, cyclic and aliphatic ketones (entries 36–39) reacted very well giving high isolated yields (85–95%). For cyclooctanone, however, the yield dropped to 50–57% (entry 40). Ketones in large rings are known to be less reactive, especially the 8 to 11-membered rings.[22,23] The reactivity of conjugated ketones was also studied and we found that they were much less reactive than aliphatic ones. Indeed, α,β-unsaturated cyclohexanone derivatives (entries 41 and 42) gave the cyanohydrin derivative **4** in only 18 and 28% yields. We tried the standard protective conditions on a substrate containing both ketone types, androstenedione (entry 43). Protection at the C-17 position was obtained in 97% yield while protection at the C-3 position was made in 37% yield. Aromatic ketones such as desoxyanisoin and 6-methoxy-1-tetralone (entries 44 and 45) are less reactive and we obtained 19 and 15% of cyanohydrin derivative, respectively. In all cases, the starting ketone was the only other compound detected. As demonstrated with the two tetralones (entries 38 and 45) and the three androstane derivatives (entries 37, 41 and 43), conjugated ketones are less reactive than unconjugated ones regarding the formation of cyanohydrin carbonate. By a judicious choice of the reaction times, this difference of reactivity could be exploited to selectively protect an unconjugated ketone in the presence of conjugated ones. The protection of aliphatic aldehydes was obtained in 72–95% yields (entries 46–49) while the protection of a benzylic aldehyde was obtained in 64% yields (entry 50). As observed with ketones, a conjugated aldehyde is less reactive than an aliphatic one. To complete the aldehyde series, cinnamaldehyde (entry 51) was treated under the protective conditions, but the formation of the cyanohydrin derivative was not observed. We rather isolated the product of a double bond reduction.

Deprotection

Ketones can be easily restored from the protective group in good yields by a number of conditions (Scheme 3 and Table 8). By dissolving the substrate in MeOH and treating that solution with a K_2CO_3 (1%) in MeOH/H_2O (3:1) solution, the cleavage of the methoxycarbonyl cyanohydrin group of compound **2** was done in 18 h and 92% yield (entry 52). Since hydrolysis of carbonate groups occurs under these conditions,[24,25] the methoxycarbonyloxy moiety of **2** was probably first hydrolyzed, followed by elimination of cyanide, and resulted with the formation of the carbonyl group of **1**. Other conditions where acetone was used as the substrate solvent gave a better result with 97% yield in 18 h (entry 53). The removal of the protective group was also accomplished by adding 4 equiv. of sodium methoxyde in MeOH (25% w/v) to the substrate dissolved in dry THF with 96% yield in only 15 min (entry 54). These later conditions were preferred because of the better solubility of studied substrates in THF and the improved rate of reaction. The deprotection of a conjugated ketone, 17β-(*t*-butyldimethylsilyl)-3-cyano-3-(methoxycarbonyloxy)-4-androstene, was also obtained under these conditions in higher than 90% yield on TLC. In opposition to ketones, aldehydes cannot be restored from the protective group in these conditions. Indeed, the basic or nucleophilic conditions used to cleave the methoxycarbonyl cyanohydrin group induce the aldol condensation of the regenerated aldehydes and limits its use as a protective group of aldehydes.

Stability of the Protective Group

The stability of *O*-substituted cyanohydrin derivatives is dependent on the cyano group and the *O*-R counter part. Thus, the *O*-methoxycarbonyl cyanohydrin derivative **2** reacts in the presence of aqueous bases, nucleophiles and some hydrides. Although it is reactive to $LiAlH_4$, the protective group can resist reduction under DIBAL-H (2 equiv.) and $NaBH_4$ (2 equiv., 2.5 h). Acid conditions such as aqueous HCl, AcOH, TfOH, and TsOH do not cleave the *O*-methoxycarbonyl cyanohydrin protective group. Results obtained also showed a very good stability with Lewis acids ($AlCl_3$, BBr_3, $BF_3{\cdot}OEt_2$) and oxidants ($NaClO_4$, CrO_3, $KMnO_4$, PCC, *t*-BuOOH, *m*-CPBA, and $NaBiO_3$). Few ketone protective groups combine stability under acid and oxidizing conditions, so the addition of a new protective group that is stable to both of these conditions should prove handy. Also, the protection and deprotection reactions



Scheme 3. Protective group cleavage model.

Table 8. Deprotection of the ketone **1** from the methoxycarbonyl cyanohydrin **2**

Entry	Solvent	Conditions	Reaction time	Yields[a] (%)
52	MeOH	K_2CO_3 (1%) in MeOH/H_2O (3:1)	18 h	92
53	Acetone	K_2CO_3 (1%) in MeOH/H_2O (3:1)	18 h	97
54	THF	NaOMe (4 equiv.)/MeOH (25% w/v)	15 min	96

[a] Isolated yields after chromatography.

Table 9. Stability of the *O*-methoxycarbonyl cyanohydrin group of **2** under usual reacting conditions

Conditions	Stability[a]
pH	
<1 (HCl/MeOH/H_2O)	S (20 h)
3 (HCl/MeOH/H_2O)	S
5 (HCl/MeOH/H_2O)	S
<1 (CF_3COOH/CH_2Cl_2)	S
1 (CF_3COOH/CH_2Cl_2)	S
3 (CH_3COOH/MeOH)	S
10 (NaOH/MeOH/H_2O)	D
13 (NaOH/MeOH/H_2O)	D
Bases	
1% K_2CO_3/MeOH/H_2O	D
NaH (4 equiv.)/THF	S
Nucleophiles	
NaOMe (4 equiv.)/THF	D (<15 min)
t-BuOK (4 equiv.)/THF	D (<1 h)
LDA (4 equiv.)/THF	D (<1 h)
Organometallics	
n-BuLi/THF	R
BuMgCl/THF	R
Hydrides	
$NaBH_4$ (2 equiv.)/MeOH	S (2.5 h)
DIBAL-H (2 equiv.)/benzene	S
$LiAlH_4$/THF	R
Oxidants	
$KMnO_4$/THF	S
CrO_3/pyridine/acetone	S
$NaClO_4$/acetonitrile	S
PCC (10 equiv.)/benzene, Δ	S
t-BuOOH (7 equiv.), PDC (cat.)/CH_2Cl_2	S
$NaBiO_3$/AcOH/H_2O/acetone	S
m-CPBA/$CHCl_3$	S
Others	
NBS/THF	S
p-Toluenesulfonic acid/benzene	S
$AlCl_3$/Benzene	S
$BF_3{\cdot}OEt_2$/THF	S
BBr_3 (3 equiv.)/CH_2Cl_2, 0°C	S

[a] Stability: S=stable, D=deprotected and R=reacted. Times in parentheses correspond to the appearance of unprotected ketone.

for this new protective group are very mild. In some cases, its mild basic or nucleophilic removal will surely be preferable to the necessary acid hydrolysis of ketals. This new protective group could be very useful for compounds that can not withstand acidic conditions (Table 9).

Conclusion

The *O*-methoxycarbonyl cyanohydrin group was easily formed at room temperature under mild conditions. To get the protective group, the carbonyl substrate and methyl cyanoformate (5 equiv.) were solubilized in a secondary alkylamine (20 equiv.)/THF mixture (1:1, v/v). Conjugated carbonyls are converted partially to the protective group, a reactivity that permits selective protection of aliphatic carbonyls vs. conjugated ones. Ketones, conjugated or not, are easily restored in good yields (>95%) by treatment with a K_2CO_3 (1%) in MeOH/H_2O solution or NaOMe in MeOH (25% w/v) solution. However, the deprotection of aldehydes is not possible under these conditions. The protective group can resist cleavage under strong acidic and oxidizing conditions. Also, it can resist reduction by DIBAL-H and $NaBH_4$ (2.5 h).

Experimental

General methods

Chemical reagents were purchased from Aldrich Chemical Company (Milwaukee, WI) except *t*-butylethylamine which was purchased from TCI America (Portland, OR). The aldehyde 3-[3′,17′β-bis (*t*-butyldimethylsilyloxy)-1′,3′, 5′(10′)-estratrien-16′α-yl]propanal (entry 48) was synthesized as reported previously.[26] Solvents were obtained from BDH Chemical (Montréal, Canada) or Fischer Chemicals (Montréal, Canada). Glassware used in anhydrous conditions was flame dried under argon current. Standard inert atmosphere techniques were used for solvent transfers by syringe. Flash-column chromatographies were performed using 230–400 mesh ASTM silica gel 60 (E. Merck, Darmstadt, Germany). Infrared spectra (IR) were recorded on a Perkin–Elmer Series 1600 FT-IR spectrometer and are reported in cm^{-1}. For some compounds, the nitrile band was too weak to be observed. The NMR spectra were recorded at 300 MHz for ^1H and 75 MHz for ^{13}C on a Brüker AC/F300 spectrometer. The chemical shifts (δ in ppm) were referenced to $CHCl_3$ (δ 7.26 and 77.0 ppm for ^1H and ^{13}C, respectively). In the characterization of diastereoisomeric mixtures, carbon peaks reported between parenthesis are carbons that were duplicated due to the presence of a new chiral center. ^1H NMR evaluated yields were based on the integration of CH_3-18 (0.91 and 0.96 ppm for **1** and **2**) and OCH_3 (3.78 and 3.85 ppm for Ph-OCH_3 and $-OCOOCH_3$) peaks on the crude products. The low resolution mass spectra (LRMS) were obtained with an API-150ex apparatus with a turbo ionspray source while the high resolution mass spectra (HRMS) were provided by the Centre Régional de Spectrométrie de Masse (Université de Montréal, Montréal, Canada).

General procedure for the formation of the *O*-methoxycarbonyl cyanohydrin from carbonyls (Table 7)

The carbonyls were dissolved in a mixture of DIPA (20 equiv.) and THF (1:1, v/v). The methyl cyanoformate (5 equiv.) was added to the solution which was stirred during 5–8 h. Then, the reaction was quenched by addition of water and the crude product was extracted twice with diethylether. The combined organic layers were thoroughly washed with HCl 10% and saturated aqueous NaCl. The organic phase was then dried over $MgSO_4$ and evaporated in vacuo. Purification of the crude products was performed by flash column chromatography with an appropriate mixture of ethyl acetate and hexanes as eluent.

17α-Cyano-3-methoxy-17β-(methoxycarbonyloxy)estra-1,3,5(10)-triene (entry 36). White solid; IR (KBr) ν 2253 (C≡N), 1754 (C=O, carbonate); ^1H NMR ($CDCl_3$) δ 0.96 (s, 3H, CH_3-18), 1.00–2.50 (m, 13H), 2.88 (m, 2H, CH_2-6), 3.78 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 6.64 (d, J=2.6 Hz,

1H, CH-4), 6.73 (dd, J_1=2.6 Hz and J_2=8.6 Hz, 1H, CH-2), 7.20 (d, J=8.6 Hz, 1H, CH-1); ^{13}C NMR ($CDCl_3$) δ 12.9, 23.1, 26.0, 27.1, 30.0, 33.6, 35.6, 38.8, 43.0, 48.1, 48.5, 55.1 (CH_3O), 55.3 (CH_3O), 85.0 (C-17), 111.6, 113.8, 118.4 (C≡N), 126.3, 131.6, 137.6, 153.9 (OCOO), 157.6; HRMS *m/z* calculated for $C_{22}H_{27}O_4N$ [M^+] 369.1940, found 369.1929.

17β-(*t*-Butyldimethylsilyloxy)-3-cyano-3-(methoxycarbonyloxy)-5α-androstane (entry 37). White solid; IR (film) ν 2255 (C≡N), 1762 (C=O, carbonate); ^{1}H NMR ($CDCl_3$) δ 0.001 and 0.005 (2 s, 6H, $(CH_3)_2Si$), 0.68 (s, 3H, CH_3-19), 0.83 (s, 3H, CH_3-18), 0.87 (s, 9H, $(CH_3)_3C-Si$), 0.90–2.50 (m, 22H), 3.54 (t, J=8.2 Hz, 1H, CH-17), 3.83 (s, 3H, CH_3O); ^{13}C NMR ($CDCl_3$) δ −4.8, −4.5, 11.4, 12.1, 18.1, 20.8, 23.5, 25.8 (3×), 27.8, 30.9, 31.2 (2×), 35.1, 35.4, 35.5, 36.8, 37.0, 43.0, 43.3, 50.4, 53.9, 55.2 (CH_3O), 76.5 (C-3), 81.7, 118.3 (C≡N), 153.1 (OCOO); HRMS *m/z* calculated for $C_{28}H_{46}O_4NSi$ [$M-H]^+$ 488.3196, found 488.3192.

2-Cyano-6-methoxy-2-(methoxycarbonyloxy)-1,2,3,4-tetrahydronaphthalene (entry 38). White solid; IR (film) ν 2241 (C≡N), 1759 (C=O, carbonate); ^{1}H NMR ($CDCl_3$) δ 2.44 (m, 2H, CH_2-3), 3.02 (m, 2H, CH_2-4), 3.30 and 3.52 (2 d, J=16.3 Hz, 2H, CH_2-1), 3.77 (s, 3H, CH_3O), 3.84 (s, 3H, CH_3O), 6.65 (d, J=2.3 Hz, 1H, CH-5), 6.74 (dd, J_1=8.3 Hz and J_2=2.3 Hz, 1H, CH-7), 6.99 (d, J=8.5 Hz, 1H, CH-8); ^{13}C NMR ($CDCl_3$) δ 25.6, 31.6, 38.0, 55.2 (CH_3O), 55.3 (CH_3O), 73.0 (C-2), 113.1 (2×), 117.9 (C≡N), 121.7, 130.1, 134.4, 153.2 (OCOO), 158.6; HRMS *m/z* calculated for $C_{14}H_{15}O_4N$ [M^+] 261.1001, found 261.0999.

4-Cyano-4-(methoxycarbonyloxy)heptane (entry 39). Colorless oil; IR (film) ν 2240 (C≡N), 1760 (C=O, carbonate); ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J=7.3 Hz, 6H, CH_3), 1.47 (m, 4H, 2×CH_2), 1.93 (m, 4H, 2×CH_2), 3.77 (s, 3H, CH_3O); ^{13}C NMR ($CDCl_3$) δ 13.6 (2×), 17.0 (2×), 38.5 (2×), 55.1 (CH_3O), 76.6 (C-4), 117.8 (C≡N), 153.1 (OCOO); LRMS *m/z* 217.3 $[M+NH_4]^+$, 200.2 $[M+H]^+$.

1-Cyano-1-(methoxycarbonyloxy)cyclooctane (entry 40). Colorless oil; IR (film) ν 2240 (C≡N), 1759 (C=O, carbonate); ^{1}H NMR ($CDCl_3$) δ 1.40–1.70 (m, 10H, 5×CH_2), 2.23 (m, 4H, 2×CH_2), 3.78 (s, 3H, CH_3O); ^{13}C NMR ($CDCl_3$) δ 20.9 (2×), 24.1, 27.2 (2×), 33.0 (2×), 55.0 (CH_3O), 77.9 (C-1), 118.6 (C≡N), 152.9 (OCOO); LRMS *m/z* 229.0 $[M+NH_4]^+$, 212.1 $[M+H]^+$.

17β-(*t*-Butyldimethylsilyloxy)-3-cyano-3-(methoxycarbonyloxy)-4-androstene (entry 41). White solid, diastereomeric mixture (in proportion 1:5); IR (film) ν 1760 (C=O, carbonate); ^{1}H NMR ($CDCl_3$+CD_3OD) δ −0.003 and 0.003 (2 s, 6H, $(CH_3)_2Si$), 0.72 (s, 3H, CH_3-18), 0.87 (s, 9H, $(CH_3)_3C-Si$), 1.06 (s, 3H, CH_3-19), 1.10–2.50 (m, 19H), 3.54 (t, J=8.2 Hz, 1H, CH-17), 3.84 (s, 3H, CH_3O), 5.57 and 5.81 (2 s, 1H, CH-4 two isomers); ^{13}C NMR ($CDCl_3$+CD_3OD) δ −5.0, −4.7, 11.1, 17.9, 18.4, 20.5 (20.7), 23.3, 25.7 (3×), 29.7, 30.7, 31.9, 33.1, 35.6, 36.6, 37.6, 43.3, 49.9 (2×), 53.6 (53.8), 55.1 (CH_3O), 72.7 (C-3), 81.4, 112.0 (114.5), 118.3 (C≡N), 153.3 (OCOO), 154.8; LRMS *m/z* 505.0 $[M+NH_4]^+$, 488.0 $[M+H]^+$; HRMS *m/z* calculated for $C_{27}H_{42}O_4NSi$ [$M-CH_3]^+$ 472.2883, found 472.2903.

1-Cyano-1-(methoxycarbonyloxy)-2-cyclohexene (entry 42). Colorless oil; IR (film) ν 2242 (C≡N), 1759 (C=O, carbonate); ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 2H, CH_2-5), 2.11 (m, 2H, CH_2-6), 2.21 (m, 2H, CH_2-4), 3.79 (s, 3H, CH_3O), 6.03 (d, J=10.1 Hz, 1H, CH-2), 6.13 (m, 1H, CH-3); ^{13}C NMR ($CDCl_3$) δ 17.4, 24.1, 33.0, 55.1 (CH_3O), 70.2 (C-1), 118.2 (C≡N), 122.1 (C-3), 136.4 (C-2), 153.2 (OCOO); HRMS *m/z* calculated for $C_9H_{11}O_3N$ [M^+] 181.0739, found 181.0736.

17α-Cyano-17β-(methoxycarbonyloxy)-4-androstene-3-one (entry 43a). White solid; IR (film) ν 2248 (C≡N), 1761 (C=O, carbonate), 1674 (C=O, α,β-unsaturated ketone); ^{1}H NMR ($CDCl_3$) δ 0.96 (s, 3H, CH_3-18), 1.18 (s, 3H, CH_3-19), 1.00–3.00 (m, 19H), 3.82 (s, 3H, CH_3O), 5.72 (s, 1H, CH-4); ^{13}C NMR ($CDCl_3$) δ 12.9, 17.3, 20.5, 23.3, 31.2, 32.4, 33.3, 33.8, 35.4, 35.6, 35.7, 38.4, 47.6, 48.9, 52.8, 55.4 (CH_3O), 84.7 (C-17), 118.2 (C≡N), 124.2 (C-4), 153.8 (OCOO), 169.8 (C-5), 199.1 (C-3); HRMS *m/z* calculated for $C_{22}H_{29}O_4N$ [M^+] 371.2097, found 371.2093.

3,17α-Dicyano-3,17β-bis(methoxycarbonyloxy)-4-androstene (entry 43b). White solid; IR (film) ν 2254 (C≡N), 1760 (C=O, carbonates); ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 3H, CH_3-18), 1.05 (s, 3H, CH_3-19), 1.00–3.00(m, 19H), 3.82 and 3.83 (2s, 6H, 2×CH_3O), 5.85 (s, 1H, CH-4); ^{13}C NMR ($CDCl_3$) δ 12.9, 17.8, 20.6, 23.2, 30.1, 31.4, 31.6, 31.8, 33.3, 35.4, 35.6, 37.3, 47.7, 48.9, 52.8, 55.2 and 55.4 (2×CH_3O), 69.8 (C-3), 84.8 (C-17), 114.3 (C-4), 118.2 and 118.9 (2×C≡N), 153.5 and 153.8 (2 x OCOO), 155.1 (C-5); HRMS *m/z* calculated for $C_{25}H_{32}O_6N_2$ [M^+] 456.2260, found 456.2265.

3,17α-Dicyano-3,17β-bis(methoxycarbonyloxy)-4-androstene (entry 43c). White solid; IR (film) ν 2255 (C≡N), 1760 (C=O, carbonates); ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 3H, CH_3-18), 1.07 (s, 3H, CH_3-19), 1.00–3.00 (m, 19H), 3.83 (s, 6H, 2×CH_3O), 5.60 (s, 1H, CH-4); ^{13}C NMR ($CDCl_3$) δ 12.9, 18.5, 20.4, 23.3, 29.7, 31.6, 31.7, 33.1, 33.2, 35.4, 35.8, 37.5, 47.7, 48.8, 52.5, 55.2 and 55.3 (2×CH_3O), 72.5 (C-3), 84.8 (C-17), 115.5 (C-4), 117.9 and 118.1 (2×C≡N), 153.2 and 153.8 (2×OCOO), 153.4 (C-5); HRMS *m/z* calculated for $C_{25}H_{32}O_6N_2$ [M^+] 456.2260, found 456.2251.

1-Cyano-1-(methoxycarbonyloxy)-1,2-(4′-methoxyphenyl)-ethane (entry 44). Colorless oil; IR (film) ν 1765 (C=O, carbonate); ^{1}H NMR ($CDCl_3$) δ 3.25 and 3.48 (2 d, J=14 Hz, 2H, CH_2-Ph), 3.76 (s, 3H, CH_3O), 3.77 (s, 3H, CH_3O), 3.82 (s, 3H, CH_3O), 6.77 (d, J=8.5 Hz, 2H), 6.89 (d, J=8.9 Hz, 2H), 6.97 (d, J=8.5 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 47.5, 55.1 (CH_3O), 55.3 (2×CH_3O), 79.8 (C-1), 113.6 (2×), 114.1 (2×), 116.9 (C≡N), 124.2, 126.6 (2×), 128.0, 132.0 (2×), 152.8 (OCOO), 159.2, 160.2; LRMS *m/z* 266.1 $[M-OCOOCH_3]^+$.

1-Cyano-5-methoxy-1-(methoxycarbonyloxy)-1,2,3,4-tetrahydronaphthalene (entry 45). Yellow oil; IR (film) ν 1759 (C=O, carbonate); ^{1}H NMR ($CDCl_3$) δ 1.99 (m, 2H,

CH_2-3), 2.56 (m, 2H, CH_2-2), 2.73 (m, 2H, CH_2-4), 3.83 (s, 6H, 2×CH_3O), 6.88 (d, J=7.8 Hz, 1H, CH-6), 7.27 (t, J=8.0 Hz, 1H, CH-7), 7.37 (d, J=8.0 Hz, 1H, CH-8); ^{13}C NMR ($CDCl_3$) δ 17.5, 22.1, 32.6, 55.2 (CH_3O), 55.5 (CH_3O), 74.0 (C-1), 110.9, 114.2, 118.5 (C≡N), 120.6, 126.4, 127.1, 131.6, 153.0 (OCOO), 157.0; LRMS m/z 279.4 $[M+NH_4]^+$.

1-Cyano-1-(4′-cyclohexenyl)-1-(methoxycarbonyloxy)-methane (entry 46). Colorless oil; IR (film) ν 2252 (C≡N), 1760 (C=O, carbonate); ^{1}H NMR ($CDCl_3$) δ 1.50 (m, 1H), 1.80–2.30 (m, 6H), 3.84 (s, 3H, CH_3O), 5.10 (d, J=6.3 Hz, 1H, CH-1), 5.66 (m, 2H, CH=CH); ^{13}C NMR ($CDCl_3$) δ 23.7, 24.0, 26.4, 36.2 (36.3), 55.7 (CH_3O), 68.6 (68.7) (C-1), 115.6 (C≡N), 124.0 (124.1), 126.9 (127.0), 154.3 (OCOO); HRMS m/z calculated for $C_{10}H_{12}O_3N$ $[M-H]^+$ 194.0817, found 194.0815.

1-Cyano-1-(methoxycarbonyloxy)-3-phenylpropane (entry 47). Colorless oil; IR (film)ν 2254 (C≡N), 1766 (C=O, carbonate); ^{1}H NMR ($CDCl_3$) 2.28 (m, 2H, CH_2-2), 2.86 (t, J=7.7 Hz, 2H, CH_2-3), 3.87 (s, 3H, CH_3O), 5.16 (t, J=7.5 Hz, 1H, CH-1), 7.19–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 30.4, 33.8, 55.7 (CH_3O), 64.1 (C-1), 116.2 (C≡N), 126.7, 128.3 (2×), 128.7 (2×), 138.8, 154.1 (OCOO); HRMS m/z calculated for $C_{12}H_{13}O_3N$ $[M^+]$ 219.0895, found 219.0886.

3,17β-Bis(*t*-butyldimethylsilyloxy)-16α-[3′-cyano-3′-(methoxycarbonyloxy)propyl]estra-1,3,5(10)-triene (entry 48). White solid; IR (film) ν 2256 (C≡N), 1763 (C=O, carbonate); ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H, $(CH_3)_2Si$), 0.19 (s, 6H, $(CH_3)_2Si$), 0.79 (s, 3H, CH_3-18), 0.90 and 0.91 (2 s, 9H, $(CH_3)_3C-Si$), 0.98 (s, 9H, $(CH_3)_3C-Si$), 1.00–2.50 (m, 16H), 2.79 (m, 2H, CH_2-6), 3.25 (d, J=7.1 Hz, 1H, CH-17), 3.87 (s, 3H, CH_3O), 5.21 (q, J=6.6 Hz, 1H, CH-3′), 6.55 (d, J=2.2 Hz, 1H, CH-4), 6.61 (dd, J_1=2.2 Hz and J_2=8.4 Hz, 1H, CH-2), 7.11 (d, J=8.4 Hz, 1H, CH-1); ^{13}C NMR ($CDCl_3$) δ −4.4, −4.1, −3.9 (2×), 12.1, 18.1 (2×), 25.7 (3×), 25.9 (3×), 26.2, 27.2, 29.1, 29.3, 29.6, 31.6, 37.3, 38.6, 43.2 (43.4), 44.0, 44.3, 48.3, 55.7 (CH_3O), 64.8 (65.0), 87.6, 116.4 (116.5) (C≡N), 117.2, 119.9, 126.1, 133.0, 137.8, 153.3, 154.3 (OCOO); LRMS m/z 659.5 $[M+NH_4]^+$, 642.5 $[M+H]^+$.

1-Cyano-1-(methoxycarbonyloxy)-3(S),7-dimethyl-6-octene (entry 49). Colorless oil; IR (film) ν 1762 (C=O, carbonate); ^{1}H NMR ($CDCl_3$) 0.96 (m, 3H, CH_3), 1.1–1.5 (m, 2H), 1.59 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.72, (m, 2H), 1.98 (m, 3H), 3.85 (s, 3H, CH_3O), 5.05 (t, J=6.4 Hz, 1H, CH-6), 5.23 (m, 1H, CH-1); ^{13}C NMR ($CDCl_3$) δ 18.9 (19.1), 25.0, 25.6, 28.5 (28.7), 36.5 (36.6), 39.1 (39.3), 51.6, 55.7 (CH_3O), 63.4 (63.8), 116.5 (116.7) (C≡N), 123.7, 131.9, 154.3 (OCOO); HRMS m/z calculated for $C_{13}H_{13}O_3N$ $[M^+]$ 239.1521, found 239.1525.

1-Cyano-1-(methoxycarbonyloxy)-1-phenylmethane (entry 50). Colorless oil; IR (film) ν 1758 (C=O, carbonate); ^{1}H NMR ($CDCl_3$) 3.87 (s, 3H, CH_3O), 6.27 (s, 1H, CH-1), 7.45 (m, 3H), 7.55 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 55.8 (CH_3O), 66.5 (C-1), 115.6 (C≡N), 127.8, 129.3 (2×), 130.6 (2×), 131.1, 154.0 (OCOO); HRMS m/z calculated for $C_{10}H_9O_3N$ $[M^+]$ 191.0582, found 191.0582.

Procedure for the cleavage of the protective group (Table 8)

Three different procedures were used to cleave the protective group. (**i**) A solution of K_2CO_3 (1%, w/v) in MeOH/H_2O (3:1) (5 mL) was added to a solution of the carbonyl **2** (0.27 mmol) in MeOH (10 mL). After 18 h at room temperature, water was added and the mixture was acidified with aqueous HCl (10%) before being neutralized with a saturated $NaHCO_3$ aqueous solution. Methanol was evaporated in vacuo and the resulting aqueous mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. (**ii**) A solution of K_2CO_3 (1%, w/v) in MeOH/H_2O (3:1) (5 mL) was added to a solution of carbonyl **2** (0.27 mmol) in acetone (10 mL). After 18 h at room temperature, water was added and the mixture was acidified with aqueous HCl (10%) before being neutralized with a saturated $NaHCO_3$ aqueous solution. Organic solvents were then evaporated in vacuo and the resulting aqueous mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. (**iii**) A solution of NaOMe (25% w/v) in MeOH (115 μL) was added to a solution of carbonyl **2** (0.14 mmol) in dry THF (5 mL). After 15 min at room temperature, water was added and the mixture was acidified with aqueous HCl (10%) before being neutralized with a saturated $NaHCO_3$ aqueous solution. The resulting aqueous mixture was then extracted with diethylether (3×). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. Purification of the crude products was performed by flash column chromatography with an appropriate mixture of ethyl acetate and hexanes as eluent.

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