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Stereoselective Synthesis of Alkenylated Malonic Diamide Using Masked Acyl Cyanide

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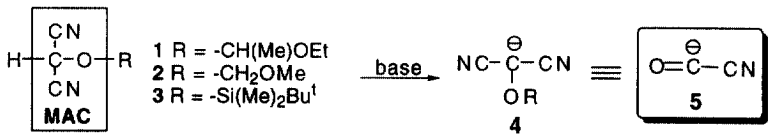
Abstract: A highly stereoselective synthesis of an alkenylated malonic diamide starting from a γ,δ-epoxy-α,β-unsaturated carboxamide was accomplished using the masked acyl cyanide (MAC: the protected hydroxymalonitrile) via palladium-catalyzed regio- and stereoselective carbon-carbon bond formation.

Keywords: cyanides; epimerization; acyl anion; palladium and compounds

In recent years, "masked acyl anion equivalents" have emerged as valuable synthetic reagents for the synthesis of important organic compounds.[1] We have recently developed a novel type of active methyne compounds **1-3** termed "masked acyl cyanide equivalents" (H-MAC-R)(Scheme 1).[2,3] Due to their reactivity and ability to function as acyl anion equivalents, the compounds **1-3** have been shown to be potentially useful reagents for the synthesis of important molecules such as 1,4-dicarbonyl compounds and dipeptides.[2-7] It should be clearly noted that the treatment of **1-3** with a base could generate a MAC-R anion **4** which could be regarded as a masked form of an acyl anion **5**.



Scheme 1

In our continuous effort to utilize these MAC compounds in the preparation of synthetically useful compounds, we had occasion to study the transformation of γ,δ-epoxy-α,β-unsaturated carbonyl compounds of type **6** into seemingly rather unstable 1,3-dicarbonyl compounds like **10** via **7**, **8**, and **9** in a regio- and stereoselective manner (Scheme 2). Since the chiral center at the α-position in alkenylated malonate derivatives **10** is highly activated by two carbonyls and a carbon-carbon double bond, controlling the stereochemistry of an R^3-CO- group in **10** in a highly stereoselective manner would be rather difficult.

The stereochemical course of diene monoepoxides with nucleophiles catalyzed by palladium(0)-complexes via η^3-allylpalladium complexes has been well-documented.[8] As shown in Scheme 2, if the epoxide group in **6** serves to control the relative stereochemistry between the hydroxy group at the δ-position and the new carbon-carbon bond at the α-position as well as the *E*-configuration of the resulting double bond in **10**, this strategy would be extremely valuable.[9,10] In addition, since **7** has an alkoxide, the H-MAC-R reagent **3** would be deprotonated by **7** to generate a η^3-allylpalladium complex **8**. Finally, the resulting MAC-R anion would attack **8** to yield the compound **9**, which can be transformed into the target 1,3-

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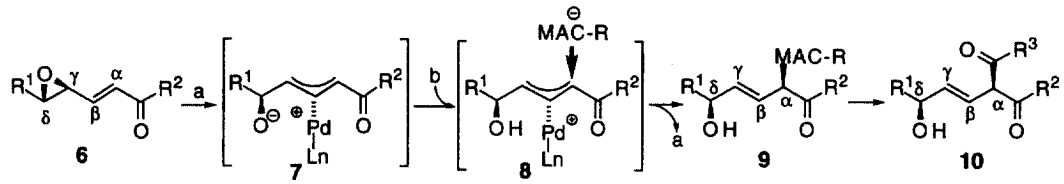
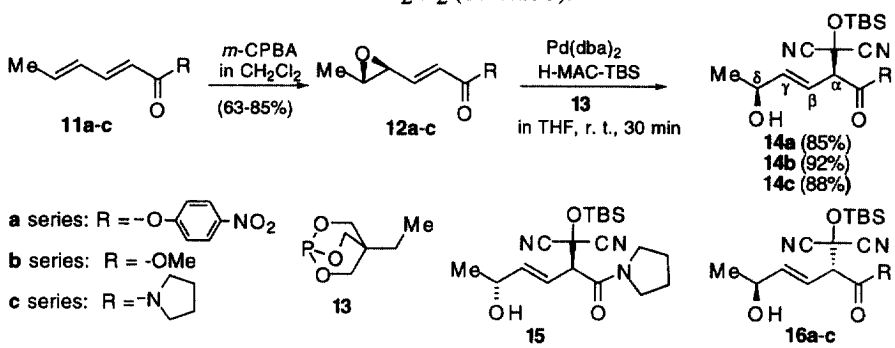
dicarbonyl compound **10**. It should be noted that the reaction steps from **6** to **9** could proceed under neutral conditions. To the best of our knowledge, a highly stereoselective route to such rather labile compounds as **10** has no precedent in the literature.



Scheme 2 R^1 = alkyl; R^2 = NR_2, OMe etc. Reagents: a = Pd(0)·Ln; b = H-MAC-R

We now detail an efficient regio- and stereoselective strategy involving the H-MAC-TBS reagent **3** for converting γ,δ-epoxy-α,β-unsaturated esters **12a-b** or the carboxamide **12c** to alkenylated MAC-TBS derivatives **14a-c** with high diastereomeric purity which are not readily accessible by other means.

The requisite substrates **12a-c** with high purity for the present study were readily prepared in synthetically acceptable yields from *trans-trans*-sorbic acid derivatives **11a-c** by selective epoxidation of one of two double bonds with m-CPBA in CH_2Cl_2 (Scheme 3).[11]



Scheme 3

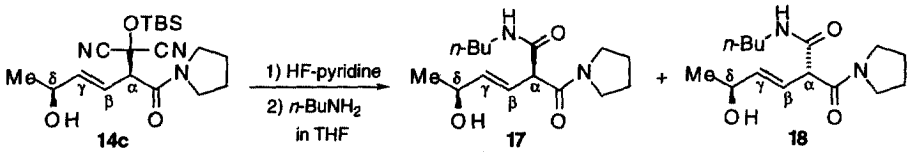
The palladium(0)-catalyzed reaction of **12a-c** with H-MAC-TBS **3** in the presence of palladium(dibenzylideneacetone) (10 mol%) and a phosphite ligand **13** (40 mol%) in THF proceeded very smoothly at room temperature within 30 min yielding the desired compounds **14a-c** regio- and stereoselectively in high yields after silica gel column chromatography with hexane/ethyl acetate (1/1). We were unable to detect any regio- or stereoisomeric compound. Typically, the diastereomeric purity of **14c** could be determined in the following manner. Oxidation of **14c** with pyridinium chlorochromate gave an α,β-unsaturated ketone which was reduced with $NaBH_4/CeCl_3$ to yield a separable 60:40 mixture of **14c** and its diastereomer **15**. Comparison of spectral data for **14c** and **15** revealed that the compound **14c** obtained from **12c** was diastereomerically pure. The *E*-configuration of all the products **14a-c** was easily established from the coupling constant (ca. 15.5 Hz) of the two olefinic protons at the β- and γ-positions by ^1H NMR analyses. The relative stereochemistry between the MAC group at the α-position and the hydroxy group at the δ-position was assumed from the well-established palladium(0)-catalyzed overall retention mechanism. X-ray diffraction analysis of **14c** confirmed the stereochemistry of the (*E*)-double bond configuration and the alkenylated carbon center.[12]

The stability of the *p*-nitrophenyl ester **14a** towards silica gel (or florisil) is low. By merely passing through a short silica gel column, **14a** gave a 1:1 mixture of two diastereomers **14a** and **16a** due to

epimerization at the α-position. Contrarily, the methyl ester **14b** could be purified by flash chromatography over silica gel. However, exposure of **14b** to triethylamine in CH_2Cl_2 for 10 min resulted in the formation of a 1:1 diastereoisomeric mixture of **14b** and **16b** as anticipated. After considerable experimentation, it was concluded that both **14a** and **14b** bearing a masked acyl cyanide group at the α-position were unsuitable for extended synthetic study due to their instability towards various conditions. In sharp contrast, the chiral center at the α-position in **14c** bearing a 1-pyrrolidinyl moiety was rather stable in comparison with the esters **14a** and **14b**. Consequently, we used **14c** for the next step.[13]

Exposure of **14c** to HF/pyridine in THF for 10 min followed by the addition of 1.2 equiv. of *n*-butylamine gave **17** along with a small amount of **18** in 43% combined yield (Scheme 4 and entry 1 in Table1). Because both the diamides **17** and **18** were stable towards florisil for a short period of time, it could be concluded that about 20% of the epimerization at the α-position occurred during the course of the transformation reaction. Next, to remove excess *n*-butyl amine and pyridine, the reaction mixture was poured into a weak acid (5% $KHSO_4$ or 5% $CuSO_4$) and subsequent usual workup and column chromatography resulted in the formation of a 93-94:7-6 mixture of **17** and **18** (Entries 2 and 3, Table 1). Thus, attempts to enhance the relative portion of **17** resulted in slight improvements. Although the combined isolated yield in the transformation reactions leaves something to be desired, we have not yet optimized all the reaction conditions.[14]

It was anticipated that the epimerization at the α-position could be suppressed by the addition of copper(I) iodide.[15,16] In actuality, a considerable suppression of the epimerization was realized by the addition of a molar equivalent of copper(I) iodide to the reaction mixture, yielding a 96-97:4-3 mixture of **17** and **18** (Entries 5 and 6, Table 1).

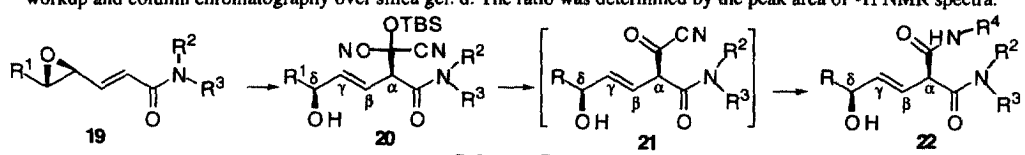


Scheme 4

Table 1. Transformation of **14c** into Alkenylated Malonic Diamides **17** and **18**

Entry	CuI (molar equiv.)	Work-up	Ratio[d] **17:18**	Combined Yield (**17** + **18**)
1	0	a	90:10	43%
2	0	b	93:07	66%
3	0	c	94:06	67%
4	1.0	a	91:09	45%
5	1.0	b	97:03	65%
6	1.0	c	96:04	63%

All the reactions were carried out in THF by exposure of **14c** to HF (1.2 molar equiv.) and pyridine (1.2 molar equiv.) at 0°C followed by treatment with *n*-butylamine (1.2 molar equiv.) for 10 min using the conditions described in Table 1. a. The reaction mixture was concentrated under reduced pressure and the residual product was chromatographed on a florisil column. b. The reaction mixture was poured into 5% aqueous $KHSO_4$ followed by usual workup and column chromatography over silica gel. c. The reaction mixture was poured into 5% aqueous $CuSO_4$ followed by usual workup and column chromatography over silica gel. d. The ratio was determined by the peak area of ^1H NMR spectra.



Scheme 5

In conclusion, we have demonstrated, for the first time, the transformation of the masked formyl cyanide molecules **20** into the corresponding dicarbonyl compounds **22** *via* acyl cyanides **21** by judicious selection of reaction conditions. It was also shown that malonic diamides of type **22** bearing a highly epimerizable chiral center was successfully synthesized in high diastereomeric purity.

References and Notes

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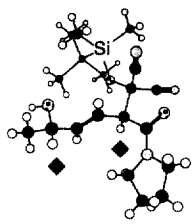
11. All compounds reported in this communication are racemic. However, only one stereoisomer of the stereoisomers is depicted for the sake of simplicity.
12. The relative stereochemistry of **14c** is determined by X-ray analysis. *R* value of the measured crystal does not satisfy the required level but is adequate for determination of the relative stereochemistry (at ◆-positions).



13. **14c**: IR (neat): 3420 (OH), 2244 (CN), 1646 (C=O), and 977 (C=C) cm^{-1}; ^{1}H-NMR (200MHz, $CDCl_3$) δ: 6.04 (1H, dd, J = 15.7, 5.0 Hz, CH_3C-C<u>H</u>=C), 5.82 (1H, dd, J = 15.7, 8.4 Hz, C=C<u>H</u>-C-C=O), 4.44 - 4.35 (1H, m, CH_3C<u>H</u>), 3.68 (1H, d, J = 8.4 Hz, C<u>H</u>C=O), 3.54-3.41 (4H, m, NCH_2×2), 2.00 - 1.84 (5H, m, NCH_2CH_2×2+O<u>H</u>), 1.32 (3H, d, J = 6.4 Hz, CH_3), 0.90 (9H, s, $SiCCH_3$×3), and 0.38 (6H, d, $SiCH_3$×2); **14c+15:** (60:40):IR (neat): 3420 (OH), 2244 (CN), 1646 (C=O), and 977 (C=C) cm^{-1}; ^{1}H-NMR (200MHz, $CDCl_3$) δ: *6.04 (0.6H, dd, J = 15.5, 4.9 Hz, CH_3C-C<u>H</u>=C), **6.02 (0.4H, dd, J = 15.6, 4.9 Hz, CH_3C-C<u>H</u>=C)**, 5.82 (0.6H, dd, J = 15.5, 8.6 Hz, C=C<u>H</u>-C-C=O), **5.80 (0.4H, dd, J = 15.6, 8.6 Hz, C=C<u>H</u>-C-C=O)***, 4.44 - 4.38 (1H, m, CH_3C<u>H</u>), 3.68 (1H, d, J = 8.6 Hz, C<u>H</u>C=O), 3.54 - 3.42 (4H, m, NCH_2×2), 2.01 - 1.81 (5H, m, NCH_2CH_2×2+O<u>H</u>), 1.32 (1.8H, d, J = 6.4 Hz, CH_3), ***1.33 (1.2H, d, J = 6.4 Hz, CH_3)***, 0.90 (9H, s, $SiCCH_3$×3), 0.38 (6H, d, $SiCH_3$×2).
14. **17**: IR (neat): 3317 (OH), 1651 (C=O), and 974 (C=C) cm^{-1}; ^{1}H-NMR (400MHz, CD_3OD) δ: 5.87 (1H, dd, J = 15.5, 8.5 Hz, CH_3C-C=C<u>H</u>), 5.75 (1H, dd, J = 15.5, 5.9 Hz, CH_3C-C<u>H</u>=C), 4.28 - 4.24 (1H, m, CH_3C<u>H</u>), 4.15 (1H, d, 8.5 Hz, C<u>H</u>C=O), 3.55 - 3.36 (4H, m, $NCH_2CH_2CH_2CH_2N$×2), 3.19 (2H, t, J = 7.1 Hz, $NHCH_2$), 2.00 - 1.85 (4H, m, $NCH_2CH_2CH_2CH_2N$×2), 1.53 - 1.43 (2H, m, $NHCH_2CH_2$), 1.39-1.30 (2H, m, $NHCH_2CH_2CH_2$), 1.23 (3H, d, J = 6.4 Hz, CH_3CH), and 0.93 (3H, t, J = 7.3 Hz, $NHCH_2CH_2CH_2$ CH_3). **17+18** (60:40) derived from a 60:40 mixture of **14c** and **15** under the same condition of entry 5 in Table 1: IR (neat) 3317 (OH), 1651 (C=O), and 974 (C=C) cm^{-1}; ^{1}H-NMR (400MHz, CD_3OD) δ 5.87 (1H, dd, J = 15.6, 8.3 Hz, CH_3C-C=C<u>H</u>), 5.75 (1H, dd, J = 15.6, 5.9 Hz, CH_3C-C<u>H</u>=C), 4.27-4.24 (1H, m, CH_3CH), ***4.14 (0.57H, d, J = 8.3 Hz, C<u>H</u>C=O)***, ***4.13 (0.43H, d, J = 8.3 Hz, C<u>H</u>C=O)***, 3.57 - 3.36 (4H, m, $NCH_2CH_2CH_2CH_2N$×2), 3.19 (2H, t, J = 6.8 Hz, $NHCH_2$), 1.99 - 1.85 (4H, m, $NCH_2CH_2CH_2CH_2N$×2), 1.52 - 1.45 (2H, m, $NHCH_2CH_2$), 1.40 - 1.29 (2H, m, $NHCH_2CH_2CH_2$), 1.23 (3H, d, J = 6.8 Hz, CH_3CH), and 0.93 (3H, t, J = 7.3 Hz, $NHCH_2CH_2CH_2CH_3$)
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