# α-Hydroxy Ketone Precursors Leading to a Novel Class of Electro-optic Acceptors

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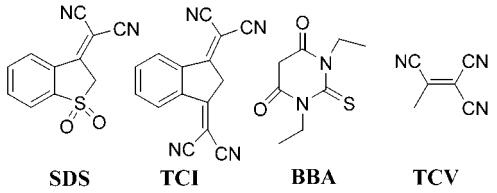
A facile high-yield synthetic route has been established for the synthesis of α-hydroxy methyl ketones. These intermediates are important precursors to the tricyanovinyldihydrofuran type of acceptor used in high $\mu\beta$ nonlinear optical chromophores. 3-Hydroxy-3-methyl-2-butanone is one of only three commercially available precursors of this type, limiting the chemist from making systematic studies of structure property relationships. This very general synthetic method allows a wide variety of α-hydroxy ketone structures to be easily made.

## Introduction

The development of polymeric second-order nonlinear optical (NLO) materials for communication applications has enjoyed great progress during the past several years. Very large macroscopic nonlinearities have been obtained both in guest/host and thermally stable poled polymers. High-speed electro-optic (EO) polymeric modulators with volt and subvolt halfwave potentials have been made.[1−5] It is generally understood that to obtain large macroscopic nonlinearities, large molecular nonlinearities must be achieved while preventing molecular aggregation. This requirement has led to significant efforts over the years to synthesize very high $\mu$-beta ($\mu\beta$) chromophores. A typical chromophore consists of an electron donor, bridge, and acceptor. Some variant of a substituted aniline is the most commonly used donor system because of its stability and electron-donating ability. Bridge systems vary from open-chain and ring-locked polyenes to various heterocyclic groups. In most cases, the heterocyclic or aromatic rings tend to have better stability both thermally and photochemically but polyenes tend to yield higher nonlinearities.[6]

The acceptor end of these chromophores has been intensively investigated over the past decade. The acceptor portion of the molecule originally started as a nitrophenyl ring[7] but was soon replaced by a host of structures with better electron-withdrawing ability and overall stability. These "strong" acceptors commonly known as SDS,[8] BBA,[9] TCI,[10] and TCV[11] all have shown




strong electron-withdrawing ability when coupled through a $\pi$ system to the same type of donors, but each acceptor has its own unique problem such as low solubility and lack of photochemical or thermal stability. One common structural feature found in all these acceptors is a very flat conjugated structure substituted with groups capable of withdrawing electron density through both inductive and resonance effects. When these acceptors are used to construct chromophores, the entire chromophore structure tends to be very flat with a large ground-state dipole moment, giving rise to large electrostatic interactions that favor antiparallel pairing of the chromophores in both the solid state and high concentrations, inhibiting the poling process. Recent studies have shown[12] when the chromophore's intermolecular dipole interactions become competitive with the externally applied poling field, the macroscopic electro-optic coefficient decreases significantly. When the concentration of these high $\mu\beta$ chromophores increases in either a guest−host or a covalently bonded polymer system, the problem becomes even more severe. Modifications to the chromophore's structure such as the addition of flexible alkyl chains or hindered three-dimensional structures at the bridge position have

(1) Ahlheim, M.; Barzoukas, M.; Bedworth, P. V.; Hu, J. Y.; Marder, S. R.; Perry, J. W.; Stahelin, C. M.; Zysset, B. *Science* **1996**, *271*, 335.
(2) Dalton, L. R. *Opt. Eng* **2000**, *139* (3), 589−595.
(3) Ma, H.; Chen, B.; Sassa, T.; Dalton, L. R.; Jen, A. K.-Y. *J. Am. Chem. Soc.* **2001**, *123*, 986.
(4) Shi, Y.; Zhang, C.; Zhang, H.; Bechtel, H. J.; Dalton, L. R.; Robinson, B. H.; Steier, W. H. *Science* **2000**, *288*, 119.
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(7) Leslie, T. M.; Choe, E. W.; DeMartino, R. N.; Hass, D. R.; Nelson, K. G.; Stamatoff, J.; Stuetz, D. E.; Teng, C. C.; Yoon, H. N. *Mol. Cryst. Liq. Cryst.* **1987**, *153*, 451.
(8) Ahlheim, M.; Barzoukas, M.; Bedworth, P. V.; Blanchard-Desce, M.; Fort, A.; Hu, Z. Y.; Marder, S. R.; Perry, J. W.; Runser, C.; Staehin, M.; Zysset, B. *Science* **1996**, *271*, 335.
(9) Gilmour, S.; Montgomery, R. A.; Marder, S. R.; Cheng, L. T.; Jen, A. K−Y. Cai, Y.; Perry, J. W.; Dalton, L. R. *Chem. Mater.* **1994**, *6*, 1603.
(10) Sun, S. S.; Zhang, C.; Dalton, L. R.; Garner, S. M.; Chen, A.; Steier, W. H. *Chem. Mater.* **1996**, *8* (11), 2539.
(11) Dorr, M.; Zentel, R.; Dietrich, R.; Meerholz, K.; Brauchle, C.; Wichern, J.; Zippel, S.; Boldt, P. *Macromolecules* **1998**, *31*, 1454.
(12) Dalton, L. R. *Opt. Eng.* **2000**, *39* (3), 589.

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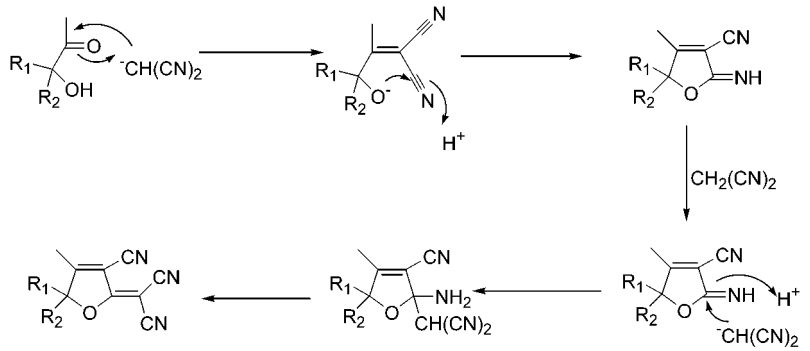
**Scheme 1**

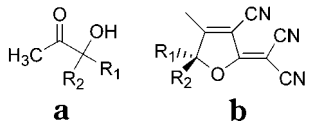


shown some effectiveness at preventing antiparallel chromophore packing.[13,14]

Our approach to solving the problem of low solubility due to intermolecular antiparallel packing is to maintain the planar conjugated acceptor $\pi$ system substituted with highly electron-withdrawing groups, while building a very anisotropic three-dimensional shape to prevent the molecules from tightly packing.

## Discussion

In this paper, we report the facile synthesis of α-hydroxy ketones leading to a novel class of electron acceptors. These acceptors show the ability to strongly withdraw electron density while facilitating steric hindrance to prevent chromophore−chromophore intermolecular interactions. The synthesis of these strong organic electron acceptors is accomplished in two steps. First, the corresponding α-hydroxy ketone (Figure 1a), also called an α-ketol, must be prepared. Second, the α-ketol is condensed with 2 equiv of malononitrile under basic conditions to create a dicyanomethylendihydrofuran (Figure 1b). The first reported synthesis of these molecules was in 1995 by the chemist Gaguik Melikian and co-workers[15] while exploring reactions aimed at the synthesis of new drug intermediates. These new compounds have a flat conjugated structure with three highly electron-withdrawing cyano groups pointing in one general direction on a furan ring structure (see structure below). If $R_1$ and $R_2$ can be independently manipulated in terms of their size, shape, and electronic character, then it should be possible to inhibit crystallization, promoting solubility while maintaining the desired electron-withdrawing properties. Melikian and co-workers synthesized five such compounds all with $R_1$ equal to methyl. Two of them were synthesized from commercially available starting materials: 3-Hydroxy-2-butanone (acetoin) where $R_2$ equals H and 3-hydroxy-3-methyl-2-butanone where $R_2$ equals methyl. The other three were synthesized from α-hydroxy ketones that were a "gift" from a co-worker. No data are supplied for the dicyanomethylendihydrofuran derivative of acetoin. We feel the acetoin derivative would not be useful as an acceptor because of $R_2$ being a hydrogen α to a highly electronegative $\pi$ system. That reactive hydrogen is most likely easily lost even with the most mild of bases.



**a** **b**

**Figure 1.**

In the structure shown in Figure 1b, the plane made by the intersection of $R_1$, $R_2$, and the $sp^3$ hybridized carbon in the ring is perpendicular to the plane of conjugation which can be used to create free space between chromophores. In fact, the data reported by Melikian and co-workers support this hypothesis in that the melting point of the compound where $R_1 = R_2 =$ methyl is significantly higher than that for the other three dicyanomethylendihydrofurans with $R_1 \neq R_2$.

The first use of this class of compound as an acceptor in a NLO chromophore was reported in 1998.[16] The authors reported a modified thiophene bridge used in conjunction with an aminophenyl donor.[13] The chromophore has been since referred to as FTC where $R_1 = R_2 =$ methyl at the furan ring acceptor end. This chromophore was reported to have an electro-optic coefficient, $r_{33}$, of 55 pm/V at 1064 nm and to be thermally stable in air to over 300 °C. Since that report, this one acceptor based on commercially available 3-hydroxy-3-methyl-2-butanone has attracted a lot of synthetic attention, with ground-breaking $r_{33}$ values being reported.[12]

As stated earlier, the synthesis of these dicyanomethylendihydrofuran compounds is the result of α-ketols reacting with 2 equiv of malononitrile under basic conditions. The mechanism of this reaction has been suggested to occur in three steps: (1) The first equivalent of malononitrile condenses with the ketone moiety and dehydrates. (2) The α-hydroxy anion is generated and attacks one of the two cyano carbons, forming an iminolactone. (3) The iminolactone reacts with a second equivalent of malononitrile, releasing ammonia to form the tricyano ring structure. (See Scheme 1.)

The questions become how general is the reaction and will all the α-ketols we make follow this mechanism? What are the effects on the ring closure reaction when $R_1$ and $R_2$ are different sizes or have different electronic properties such as electron donation or withdrawal? Will

(13) He, M.; Zhu, J.; Harper, A. W.; Sun, S. S.; Dalton, L. R.; Garner, S. M.; Chen, A.; Steier, W. H. *ACS Symp. Ser.* **1998**, *695*, 258.

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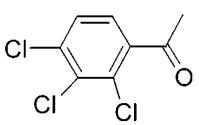
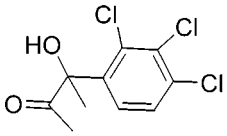
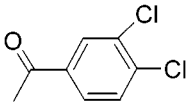
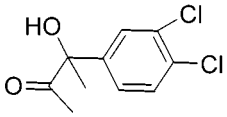
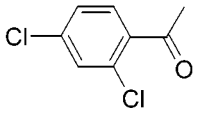
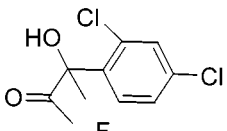
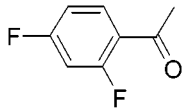
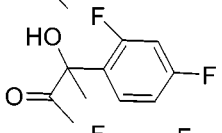
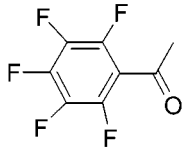
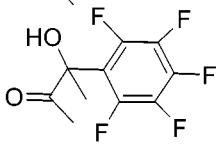
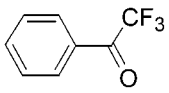
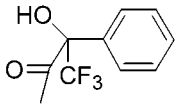
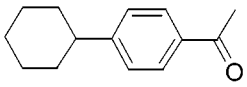
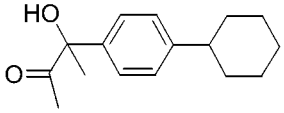
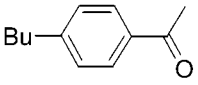
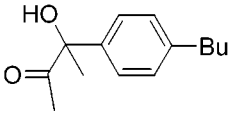
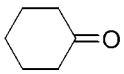
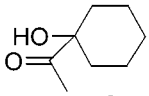
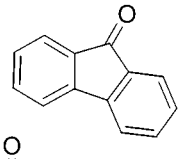
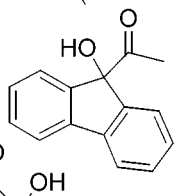
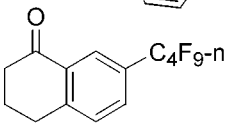
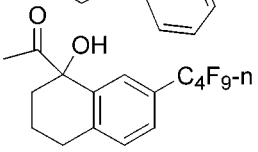
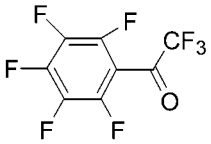
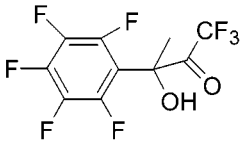
(16) Wang, F.; Ren, A. S.; He, M.; Harper, A. W.; Dalton, L. R.; Garner, S. M.; Zhang, H.; Chen, A.; Steier, W. H. *Polym. Mater. Sci. Eng.* **1998**, *78*, 42.

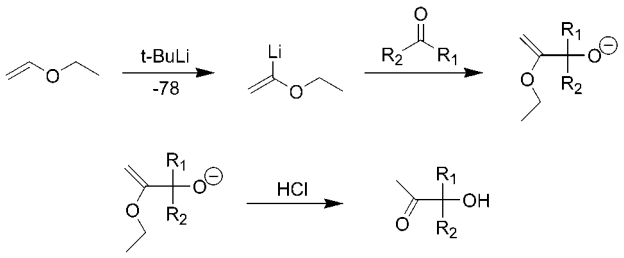
**Table 1. Ketones to Ketols**

| ketones | α-ketols | number | yields |
|---|---|---|---|
|  |  | 1 | 66% |
|  |  | 2 | 52% |
|  |  | 3 | 68% |
|  |  | 4 | 69% |
|  |  | 5 | 71% |
|  |  | 6 | 95.7% |
|  |  | 7 | 82% |
|  |  | 8 | 87% |
|  |  | 9 | 82.8% |
|  |  | 10 | 75% |
|  |  | 11 | 72% |
|  |  | 12 | 50.5% |

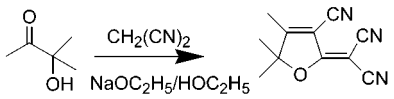
the α-ketol form a spiro ring juncture when $R_1$ and $R_2$ are connected together or will it prohibit formation of the tricyanofuran ring? What bases are the most effective for high yields? To answer these questions, a large number of α-ketols have been synthesized following a modification of the method reported by Baldwin et al.[17]

Ethyl vinyl ether was reacted with *t*-butyllithium at −78 °C and the vinyl anion formed. Various ketones were then added to the vinyllithium solution, with the anion quickly reacting with the pro-chiral ketone (when $R_1 \neq R_2$). After acid hydrolysis, the racemic α-ketols were obtained as shown in Scheme 2.

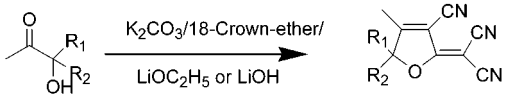
**Scheme 2**




**Scheme 3**




**a**




**b**

Table 1 lists all the α-ketols synthesized through this method along with their isolated yields. Originally, conversion of the α-ketol to the corresponding furan was run using the conditions outlined by Melikian using an equivalent of sodium ethoxide in ethanol solution. We found that in our case the sodium ethoxide conditions gave a lot of byproducts. Because the mechanism indicates the amount of base required is only catalytic, we decided to look at the effect of keeping the amount of base to a minimum versus adding a stoichiometric equivalent. We selected three new bases, anhydrous $K_2CO_3$/18-crown-6, $LiOC_2H_5$, and LiOH, to study the effects on the ring closure reaction. All gave very good results. When anhydrous potassium carbonate was used as the base, an equivalent of anhydrous $K_2CO_3$ was added and a minimum of crown ether used as catalyst. Whether the amount of base was added as an equivalent or catalytic amount for the lithium bases, no difference was observed. We found when $LiOC_2H_5$ and LiOH were used as bases, since only a catalytic amount was required, a 5−10% molar equivalent of base gave very good results.

Melikian's original conditions are shown in Scheme 3a with the modified conditions shown in Scheme 3b.

A previous report[15] has suggested that the α-ketols react with malononitrile through a Knoevenagel condensation, followed by the hydroxyl group attacking one of the nitriles to form an iminolactone intermediate. This intermediate reacts with malononitrile again, releasing ammonia gas and forming the final product. Our experiments support this mechanism. From all of the condensation reactions that successfully lead to a dicyanofuran, we have been able to observe ammonia gas being produced during the reaction. We have also

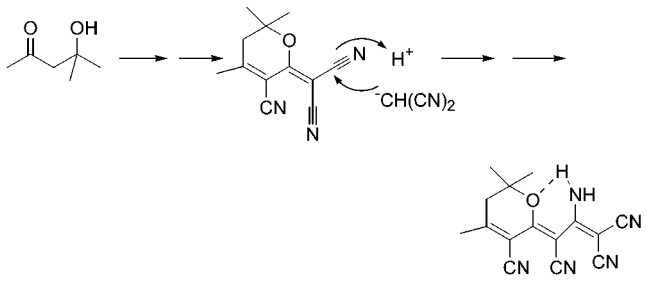


**Figure 2.**

tested the generality of the reaction by reacting a *β*-ketol with malononitrile using the same conditions. We believe that the first steps of the mechanism are followed, but the last are not since the final product is different as shown in Figure 2.

We feel this is due to the formation of a very stable six-membered ring that can react with malononitrile a third time to form a thermally favorable hydrogen-bonded double-ring structure with hydrogen bonding between the amino group and ring oxygen as shown. $^1$H NMR, $^{13}$C NMR, and MS analyses are all consistent with this proposed structure.

We have also noticed that the electronic properties of $R_1$ and $R_2$ have a large impact on the ring closure. If the hydroxyl group attacking the nitrile function is the crucial step in forming the desired product, the stronger nucleophilic tendency the oxygen anion has, the better yield of ring closure should be. When $R_1$ and $R_2$ are electron-donating groups, the oxygen anion should favor ring closure since it is destabilized and therefore more reactive. When $R_1$ and $R_2$ are electron-withdrawing groups, the reaction should be slower and ring closure more difficult since the anion is stabilized and less reactive. Our experiments support this hypothesis. A comparison of both the rate and yield of ring closure for 3-hydroxy-3-[4′-*n*-butylphenyl]-2-butanone **8** with 3-hydroxy-3-[pentafluorophenyl]-2-butanone **5** has been made. We reacted both α-ketols under identical conditions to synthesize the corresponding acceptors. We found **8** with the electron-rich *p*-butylphenyl group to be more reactive under the same conditions with respect to **5** with the pentafluorophenyl ring. The yields obtained for the corresponding furans after 24 h were significantly different. **8** gave a much higher yield (69%) relative to **5** (19%). We also noticed that steric hindrance seems to play a role in this reaction. A comparison of 3-hydroxy-3-[2′,4′-dichlorophenyl]-2-butanone **3** and 3-hydroxy-3-[3′,4′-dichlorophenyl]-2-butanone **2** under the same reaction conditions shows **2** is much faster to form product (26%) than **3** (16%) after the same reaction time. The difference between them is the position of the two chlorine atoms on the benzene ring. Both have a chlorine in the para position but **3** has the second chlorine in the ortho position rather than the meta position as in **2**. The chlorine in the ortho position appears to hinder ring closure more than expected from simple electronic changes. Reasonable yields of acceptors from α-hydroxy ketone **3** required 36 h at reflux (16.7%) while **2** (25.9%) only needed 24 h. When electron-withdrawing effects are combined with steric hindrance, the ring closure reaction does not proceed and no corresponding furan was formed. This was found to be the case for 3-hydroxy-3-[2′,3′,4′-trichlorophenyl]-

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(19) Koike, T.; Murata, K.; Ikariya, T. *Org. Lett.* **2000**, *2* (24), 3833.
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2-butanone **1.** This α-ketol was reacted under reflux conditions for 36 h and no trace of the furan acceptor was detected. However, if one compares compound **5** with a pentafluorophenyl ring to the trichlorophenyl analogue **1**, compound **5** with the more electron-withdrawing ring forms the furan derivative in about 19% yield where the other does not. Therefore, the effect must not be due to electronic factors alone.

The choice of catalyst is also very important. When $NaOC_2H_5$ or $K_2CO_3$ was used, some reactions, particularly with the α-ketol bearing electron-withdrawing functions, did not form the furan derivative or a very poor yield was obtained. But when the base was changed to $LiOC_2H_5$, the ring closure reaction was more successful. We believe that the lithium ion forms a strong lithium−nitrogen complex with the nitrile nitrogen which facilitates the ring closure reaction. Table 2 lists the structures and isolated yields obtained from the lithium-mediated reaction.

All of these acceptors in Table 2 have a structure where the $sp^3$-hybridized carbon in the ring forces the two R groups to be above and below the plane of the ring. As can be seen from Table 2, the structures can bear very different and very large groups as seen for structures **19** and **20** where one R group is methyl and the other a para-substituted benzene ring. The synthetic method currently used produces a racemic mixture when $R_1$ and $R_2$ are different. We have not separated the product into pure enantiomers as of yet nor have we attempted to run the reactions under conditions that would favor one enantiomer over the other. We are currently pursuing those experiments. Spiro junctions also can be formed as evidenced in structures **21**, **22**, and **23**, showing the overall versatility of this synthetic route. Because the two groups can be both large and very different, we believe this will facilitate the separation of the highly dipolar tricyano acceptor structures. Physical separation between molecules should be a great benefit to the solubility as well as other physical properties of the final chromophore.

## Conclusion

A dozen new α-ketols have been synthesized and these new α-ketols have all been converted into new NLO acceptors except one that does not ring close for electronic and steric reasons. The reaction mechanism of the ring closure has been discussed with respect to the yield of the final product and speed of reaction. All of the acceptors have a structure where the $sp^3$-hybridized carbon in the ring forces the two R groups above and below the plane of the ring we believe resulting in increasing the free space around the highly polar tricyanofuran ring structure, preventing chromophore−chromophore electrostatic interactions. The fact that the final product is left as a racemic mixture may also aid in the final chromophore's solubility. By using our modified synthetic method, a wide variety of ketones can be converted to the corresponding α-ketol. Electron-rich substituents at the $R_1$ and $R_2$ positions seem to enhance ring closure to the tricyanofuran ring structure, while electron-withdrawing and particularly stericly large groups appear to hamper the ring closure reaction.

## Experimental Section

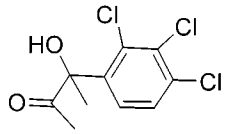
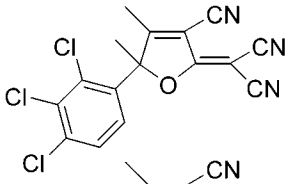
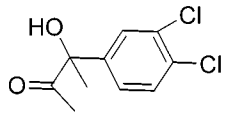
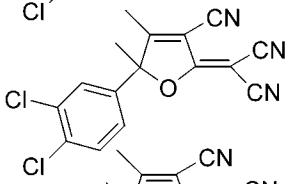
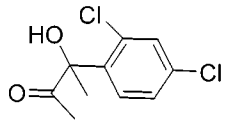
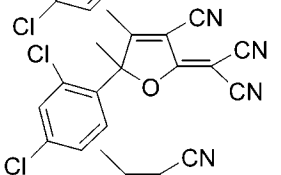
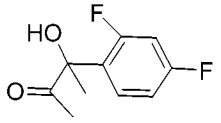
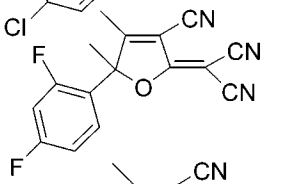
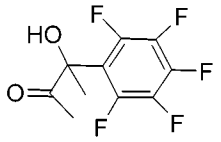
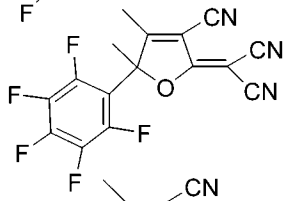
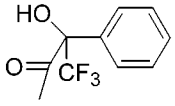
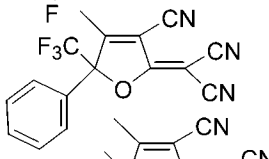
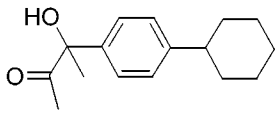
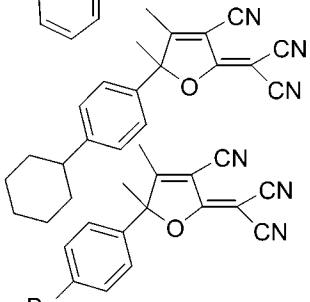
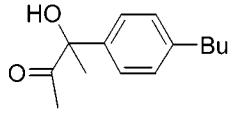
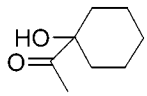
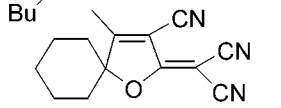
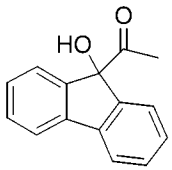
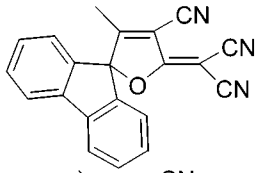
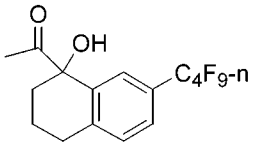
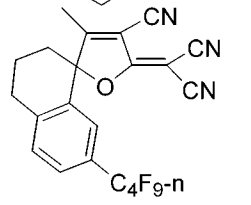
**General Information.** $^1H$ NMR, $^{13}C$ NMR, and $^{19}F$ NMR were obtained with a Varian Unity Inova 300-MHz system. TMS was used as the internal standard. $CDCl_3$ was used as solvent unless specified otherwise. Gas chromatography/mass spectrometry (GC/MS) data were obtained using a Varian Saturn 200 system fitted with a J&W Scientific DB-5MS 30 m × 0.252 mm capillary column with He at 1.0 mL/min as the carrier gas. HPLC data were collected using a Waters HPLC instrument consisting of (1) a Waters Alliance 2690 pump system, (2) a Waters Model 996 photodiode array detector, and (3) Nova-Pak $C_{18}$ column (3.9 × 150 mm) with a mobile phase flow rate of 0.5 mL/min. The mobile phase was acetonitrile water 60/40 for samples 15−18, 22, and 23, acetonitrile water 40/60 for samples 21 and 24, acetonitrile water 70/30 for sample 20, and acetonitrile water 20/80 for sample 19. The HPLC purities reported are for the peak areas as determined at the reported wavelength given in parentheses using Millenium$^{32}$/GPC software. Melting points were obtained from a Mel-Temp 3.0 device and are uncorrected. All of the starting ketones were purchased and used without any further purification.

**General Procedure for the Synthesis of the α-Ketols.** Typically, 0.1 mol of ethyl vinyl ether was dissolved into 100 mL of dry THF in a round-bottom flask fitted with a Claisen head, reflux condenser, and addition funnel. The solution cooled to −78 °C under argon and 0.095−0.1 mol of *tert*-butyllithium as a solution in pentane was transferred to the addition funnel by cannula under argon and added dropwise. The solution was allowed to slowly warm to −10 °C followed by the dropwise addition of the appropriate ketone (0.05 mol) as a concentrated solution in dry THF. The final reaction mixture was stirred overnight at room temperature. Afterward, enough HCl methanol and water solution was added to just acidify the reaction solution to litmus. When the reaction mixture became acidic, a sudden change of color was always observed. The acidic solution was stirred for an additional 2 h at room temperature followed by concentration on a rotary evaporator by removing the majority of the THF. Ethyl ether (50 mL × 3) was used to extract the organic α-ketols from the concentrate. The combined organic solutions were washed with sodium bicarbonate solution, brine, and water followed by drying the organic layer over anhydrous $MgSO_4$. After the solvent was evaporated, the α-ketols were obtained in pure form by either vacuum distillation or column chromatography (5% ethyl acetate in hexane on 60−200-mesh silica gel).

**General Procedure of Synthesis of Acceptors.** Typically, 0.01 mol of the α-ketol and 0.02 mol of malononitrile were dissolved into THF. A 5% molar amount (based on ketol) of $LiOC_2H_5/HOC_2H_5$ solution was added to the reaction mixture. The mixture was refluxed overnight followed by concentration on the rotary evaporator. The residue was dissolved in methylene chloride. This organic mixture was then washed with brine and water, followed by drying the organic layer over anhydrous $MgSO_4$. After the solvent was evaporated, the crude product was recrystallized from ethyl alcohol to give pure acceptor.

**3-Hydroxy-3-[2′,3′,4′-trichlorophenyl]-2-butanone (1).** Following the general procedure, ethyl vinyl ether (12.96 g, 0.18 mol) was reacted with *tert*-butyllithium (0.18 mol, 105 mL, 1.7 M in pentane) at −78 °C in 100 mL of dry tetrahydrofuran (THF). The solution was allowed to slowly warm to −10 to 0 °C, followed by the dropwise addition of 2′,3′,4′-trichloroacetophenone (20 g, 0.09 mol) as a concentrated solution in dry THF. The final reaction mixture was stirred overnight at room temperature. Enough acid solution (60% methanol, 20% water, and 20% HCl by volume) was added to just acidify the reaction solution to litmus. When the reaction mixture became acidic, it was stirred for an additional 2 h at room temperature followed by concentration on a rotary evaporator by removing the majority of the THF. Ethyl ether (50 mL × 3) was then used to extract the organic material from the concentrate. The combined ether solutions were

**Table 2. Acceptor Synthesis**[a]

| α-ketols | acceptor | number | yields |
|---|---|---|---|
|  |  | 13 | 0% |
|  |  | 14 | 25.9% |
|  |  | 15 | 16.7% |
|  |  | 16 | 37.9% |
|  |  | 17 | 19.2% |
|  |  | 18 | 25.9% |
|  |  | 19 | 71.7% |
|  | | 20 | 69% |
|  |  | 21 | 67.5% |
|  |  | 22 | 45.0% |
|  |  | 23 | 11.86 |

[a] Note: All yields reported in Table 2 are the isolated yields.

washed with sodium bicarbonate solution (100 mL), brine (2 × 100 mL), and water (2 × 100 mL), followed by drying the organic layer over anhydrous $MgSO_4$. Pure compound **1** was obtained by vacuum distillation at 124−126 °C/0.2 mbar; collecting 15.84 g (yield 66.3%). mp 49−51 °C. $^1$H NMR: $\delta$ 7.54 (d, 1H), 7.42 (d, 1H), 4.24 (OH, s, 1H), 2.099 (s, 3H), 2.097 (s, 3H). $^{13}$C NMR: 207.888, 140.145, 133.983, 132.774, 132.686, 128.256, 126.302, 79.447, 24.567, 23.964. GC/MS: 249 (M −

OH), 43 (base, 100%). Purity by GC peak area 97.33%. Retention time: 13.866 min.

**3-Hydroxy-3-[3′,4′-dichlorophenyl]-2-butanone (2).** Following the above general procedure, To ethyl vinyl ether (27.1 g, 0.376 mol), *t*-butyllithium (221 mL, 0.376 mol), and THF (150 mL) was added 3′,4′-dichloroacetophenone (30.5 g, 0.188 mol). Vacuum distillation gave pure **2** at 105−107 °C/0.4 mbar. Yield: 19.1 g (51.6%). $^1$H NMR: $\delta$ 7.567 (d, 1H), 7.463 (d, 1H), 7.298 (d, 1H), 4.452 (s, OH, 1H), 2.114 (s, 3H), 1.750 (s, 3H). $^{13}$C NMR: 208.45, 141.89, 133.06, 132.44, 130.65, 128.33, 125.52, 79.37, 24.32, 23.42. GC/MS: 216 (M − OH, base, 100%), 232 ($M^+$), 43 ($COCH_3$). RT: 11.72 min. Purity by GC peak area 97.81%.

**1-Hydroxy-1-methyl-1-[2′,4′-dichlorophenyl]-2-propanone (3).** Ethyl vinyl ether (38.2 g, 0.53 mol), *tert*-butyllithium (311 mL, 0.53 mol), THF (150 mL), and 2′,4′-dichloroacetophenone (50 g, 0.265 mol) were reacted as above. Vacuum distillation gave pure **3** at 120−122 °C/ 0.5 mbar. Yield: 61.6 g (68.2%). $^1$H NMR: $\delta$ 7.593 (d, 1H), 7.404 (d, 1H), 7.335 (dd, 1H), 4.255 (s, 1H, OH), 2.087 (s, 3H, $CH_3$), 1.713 (s, 3H, $CH_3$). $^{13}$C NMR: 208.78, 137.77, 135.25, 134.39, 131.04, 129.38, 127.49, 79.42, 25.15, 24.19. GC/MS: 216 (M − OH, base, 100%), 43 ($COCH_3$). RT: 11.495 min. Purity by GC peak area 96.62%.

**3-Hydroxy-3-[2′,4′-difluorophenyl]-2-butanone[18,19] (4).** Ethyl vinyl ether (18.5 g, 0.256 mol), *tert*-butyllithium (150 mL, 0.256 mol), THF (200 mL), and 2′,4′-difluoroacetophenone (20 g, 0.128 mol) were reacted according to the general procedure. Pure **4** was obtained by column chromatography (5% ethyl acetate on 60−200-mesh silica gel) to give 16.1 g. Yield: 69%. $^1$H NMR: $\delta$ 7.551 (d, 1H), 6.936 (dd, 1H), 6.821 (d, 1H), 4.443 (s, 1H, OH), 2.133 (s, 3H), 1.744 (s, 3H). $^{19}$F NMR: −108.89 (d, 1F), −110.27 (d, 1F). $^{13}$C NMR: 208.58, 163.21, 160.90, 129.22, 125.26, 111.60, 104.91, 77.71, 24.31, 23.57. GC/MS: 183 (M − OH, base, 100%), 157 (M − $COCH_3$). RT: 6.27 min. Purity by GC peak area 100%.

**3-Hydroxy-3-[pentafluorophenyl]-2-butanone (5).** Ethyl vinyl ether (20 g, 0.278 mol), *tert*-butyllithium (140 mL, 0.238 mol), THF 100 mL, and 2′,3′,4′,5′,6′-pentafluoroacetophenone (25 g, 0.119 mol) were reacted following the general procedure. The final product **5** was purified by vacuum distillation at 73−75 °C/0.4 mbar. Yield: 71.2%. $^1$H NMR: $\delta$ 4.529 (s, 1H, OH), 2.228 (s, 3H, Me), 1.837 (t, 3H, Me split by F). $^{13}$C NMR: 206.99, 148.48, 145.09, 143.79, 140.53, 137.39, 137.16, 116.22, 26.25, 24.39. $^{19}$F NMR: −137.94 (d, 2F), −152.21 (m, 1F), −160.26 (m, 2F). GC/MS: 237 (M − OH, base, 100%), 43 ($COCH_3$). RT: 5.67 min. Purity by GC peak area 97.84%.

**3-Hydroxy-3-phenyl-4,4,4-trifluoro-2-butanone (6).** Ethyl vinyl ether (20 g, 0.278 mol), *tert*-butyllithium (160 mL, 0.278 mol), THF (100 mL), and 2,2,2-trifluoroacetophenone (24.4 g, 0.14 mol) were reacted according to the general procedure. The corresponding ketol **6** was purified by column chromatography (10% ethyl acetate in hexane on 60−200-mesh silica gel) to give 29.2 g. Yield: 95.7%. $^1$H NMR: $\delta$ 7.573−7.425 (m, 5H), 4.968 (s, 1H, OH), 2.324 (s, 3H, Me). $^{13}$C NMR: 201.796, 133.480, 129.650, 129.123 (2C), 126.635 (2C), 123.743, 82.625, 25.230. GC/MS: 202 (M − O), 106 (base, 100%). 43 ($COCH_3$). RT: 4.92 min. Purity by GC peak area 98.39%.

**3-Hydroxy-3-[4′-cyclohexylphenyl]-2-butanone (7).** Ethyl vinyl ether (35.3 g, 0.49 mol), *tert*-butyllithium (200 mL, 0.34 mol), THF (150 mL), and 4′-cyclohexylacetophenone (50 g, 0.27 mol) were reacted according to the general procedure. The corresponding α-ketol **7** was collected through column chromatography (5% ethyl acetate in hexane on 60−200-mesh silica gel). **7** yielded 82%, 49.5 g of product. After cooling, **7** becomes a waxy solid with a melting point of 52−53 °C. $^1$H NMR: $\delta$ 7.350 (d, 2H), 7.211 (d, 2H), 4.472 (s, 1H, OH), 2.450 (m, 1H, ring), 2.087 (s, 3H, Me), 1.842 (m, 4H, ring), 1.760 (s, 3H, Me), 1.390−1.251 (m, 6H, ring). $^{13}$C NMR: 210.021, 148.143, 138.970, 127.302 (2C), 126.054 (2C), 79.943, 44.343, 34.560, 34.545, 27.036 (2C), 26.307, 24.266, 23.697. GC/MS: 247 ($M^+$), 229 ($M^+$ − OH), 204 ($M^+$ − $COCH_3$, base, 100%), 43 ($COCH_3$). RT: 15.28 min. Purity by GC peak area 96.00%.

**3-Hydroxy-3-[4′-*n*-butylphenyl]-2-butanone (8).** Ethyl vinyl ether (19.5 g, 0.271 mol), *tert*-butyllithium (159 mL, 0.271 mol), THF (100 mL), and 4′-butylacetophenone (24 g, 0.136 mol) were reacted following the general procedure. Pure compound **9** was obtained through column chromatography (5% ethyl acetate in hexane on 60−200-mesh silica gel) to afford 26 g. Yield: 86.7%. $^1$H NMR: $\delta$ 7.339 (d, 2H), 7.183 (d, 2H), 4.492 (s, 1H, OH), 2.596 (t, 2H, $CH_2$), 2.071 (s, 3H, Me), 1.748 (s, 3H, Me), 1.610−1.328 (m, 4H, $CH_2$), 0.916 (t, 3H, Me). $^{13}$C NMR: 209.98, 142.96, 138.87, 128.86, 125.99, 79.93, 35.84, 33.63, 24.25, 23.61, 22.47. GC/MS: 203 (M − OH, base, 100%), 43 ($COCH_3$). RT: 12.09 min. Purity by GC peak area 97.17%.

**1-Hydroxy-1-cyclohexylethanone[18] (9).** Ethyl vinyl ether (28.8 g, 0.4 mol), *tert*-butyllithium (235 mL, 0.4 mol), THF (150 mL), and cyclohexanone (30 g, 0.31 mol) were reacted according to the general procedure. Pure compound **9** was obtained by vacuum distillation at 46−48 °C/0.3 mbar to afford 36 g. Yield: 82.8%. $^1$H NMR: $\delta$ 4.456 (s, 1H, OH), 2.240 (s, 3H, Me), 1.800−1.200 (m, 11H, ring). $^{13}$C NMR: 212.40, 33.92, 25.78, 24.36, 20.57. GC/MS: 142 ($M^+$), 125 ($M^+$ − OH, base, 100%). RT: 4.42 min. Purity by GC peak area 100%.

**9-Hydroxy-9-acetyl-fluorene[20,21] (10).** Ethyl vinyl ether (14.4 g, 0.2 mol), *tert*-butyllithium (118 mL, 0.2 mol), THF (100 mL), and 9-fluorenone (18 g, 0.1 mol) were reacted together as outlined in the general procedure. The α-ketol **10** was obtained through column chromatography (10% ethyl acetate in hexane on 60−200-mesh silica gel) and afforded 16.8 g. Yield: 75%. mp 106.9−108.4 °C. $^1$H NMR: $\delta$ 7.747 (m, 2H), 7.474−7.420 (m, 2H), 7.327 (m, 4H), 5.092 (s, 1H, OH), 1.641 (s, 3H, Me). $^{13}$C NMR: 206.837, 146.334 (2C), 142.278 (2C), 130.598 (2C), 129.224 (2C), 124.852 (2C), 121.509 (2C), 89.428, 23.201. GC/MS: 224 ($M^+$), 208 (M − O, base, 100%), 181 ($M^+$ − $COCH_3$). RT: 13.87 min. Purity by GC peak area 94.84.

**1-Hydroxy-1-acetyl-7-[1′,1′,2′,2′,3′,3′,4′,4′,4′-nonafluorobutyl]tetralin (11).** Ethyl vinyl ether (8 g, 0.11 mol), *tert*-butyllithium (65 mL, 0.11 mol), THF (50 mL), and 7-perfluorobutyl-1-tetralone (20 g, 0.055 mol) were reacted as given in the general procedure. The product **11** was obtained through column chromatography (15% ethyl acetate in hexane on 60−200-mesh silica gel) to give 16.0 g. Yield: 71.4%. $^1$H NMR: $\delta$ 7.462 (d, 1H), 7.340 (d, 1H), 7.144 (d, 1H), 4.622 (s, 1H, OH), 2.045 (s, 3H, Me). $^{13}$C NMR: 210.154, 142.370, 136.494, 130.355, 127.520, 126.882, 126.528, 117.561, 115.687, 110.365, 109.079, 78.577, 34.514, 29.802, 24.590, 18.672. GC/MS: 391 (M − OH, base, 100%), 43 ($COCH_3$). RT: 10.94 min. Purity by GC peak area 100%.

**1,1,1-Trifluoro-3-hydroxy-3-pentafluorophenyl-2-butanone (12).** Ethyl vinyl ether (6.5 g, 0.09 mol), *tert*-butyllithium (53.0 mL, 0.09 mol), THF (40 mL), and octafluoroacetophenone (12.0 g, 0.045 mol) were reacted following the general procedure. The product **12** was obtained through column chromatography (10% ethyl acetate in hexane on 60−200-mesh silica gel) to give 7.0 g of liquid oil. Yield: 50.5%. $^1$H NMR: $\delta$ 4.962 (s, 1H, OH), 2.392 (s, 3H, Me). $^{19}$F NMR: −73.900 (3F), −135.909 (2F), −149.739 (1F), −159.707 (2F). $^{13}$C NMR: 198.087, 145.836 (2C), 142.501, 138.372 (2C), 122.468, 109.854, 79.626, 25.047. GC/MS: 309 (M), 291($M^+$ − OH), 265 ($M^+$ − $COCH_3$), 196 (base, 100%). RT: 3.92 min. Purity by GC peak area.

**2-Dicyanomethylene-3-cyano-4,5-dimethyl-5-[3′,4′-dichlorophenyl]-2,5-dihydrofuran (14).** Compound **2** (15 g, 0.064 mol), malononitrile (8.5 g, 0.129 mol), and lithium ethoxide (3.2 mL, 3.2 mmol, 1 M solution in ethanol) were stirred in 80 mL of THF solution and allowed to boil under reflux conditions overnight. The solution was concentrated by removing the majority of the THF on a rotary evaporator under aspirator vacuum. The remaining residue was taken up in methylene chloride and washed with brine (2 times) and then DI water (2 times). The organic layer was dried over anhydrous $MgSO_4$ and filtered and the solvent removed. The crude product was recrystallized from denatured alcohol to yield the targeted compound **14** to give 5.5 g. Yield: 25.9%. mp 226.4−228.6. $^1$H NMR: $\delta$ 7.579 (d, 1H), 7.324 (d, 1H), 7.070 (dd, 1H), 2.254 (s, 3H, Me), 2.001 (s, 3H, Me). $^{13}$C NMR: 180.253, 175.015, 135.676, 134.630, 134.382, 131.982, 127.552, 124.595,

110.580, 109.966, 108.810, 105.822, 100.107, 60.573, 22.894, 22.894, 14.637. Purity by HPLC, $\lambda = 300$ nm, 100%.

**2-Dicyanomethylene-3-cyano-4,5-dimethyl-5-[2′,4′-dichlorophenyl]-2,5-dihydrofuran (15).** Compound **3** (6.8 g, 0.029 mol), malononitrile (3.8 g, 0.058 mol), lithium ethoxide (1 mL, 1 mmol), and THF (10 mL) were mixed and boiled at reflux for 36 h. Following the workup above, solid product was obtained from recrystallization in ethanol to give 1.6 g of **15**. Yield: 16.7%. mp 239−240 °C. $^1$H NMR: $\delta$ 7.501 (d, 1H), 7.472 (s, 1H), 7.427 (dd, 1H), 2.194 (s, 3H, Me), 2.032 (s, 3H, Me). $^{13}$C NMR: 180.244, 176.047, 138.409, 135.059, 132.545, 130.484, 128.649, 128.359, 110.807, 110.281, 109.033, 107.339, 99.563, 60.479, 25.521, 14.494. Purity by HPLC, $\lambda = 300$ nm, 88.05%

**2-Dicyanomethylene-3-cyano-4,5-dimethyl-5-[2′,4′-difluorophenyl]-2,5-dihydrofuran (16).** Compound **4** (8 g, 0.04 mol), malononitrile (5.3 g, 0.08 mol), and lithium ethoxide (2 mL, 2 mmol) were refluxed in 50 mL of THF overnight. After workup, pure **16** was obtained by crystallization from ethanol. It afforded 4.5 g. Yield: 37.9%. mp 219.0−221.4. $^1$H NMR: $\delta$ 7.441 (d, 1H), 7.066 (dd, 1H), 6.945 (d, 1H), 2.274 (s, 3H, Me), 2.041 (s, 3H, Me). $^{13}$CNMR: 179.93, 175.19, 164.54, 160.89, 129.18, 117.28, 112.69, 110.61, 109.99, 108.78, 105.95, 105.68, 98.41, 59.74, 23.26, 14.20. $^{19}$F NMR: −104.81 (d, 1F), 107.294 (d, 1F). Purity by HPLC, $\lambda = 300$ nm, 100%.

**2-Dicyanomethylene-3-cyano-4,5-dimethyl-5-[2′3′4′5′6′-pentafluorophenyl]-2,5-dihydrofuran (17).** Compound **5** (10.0 g, 0.04 mol), malononitrile (5.3 g, 0.08 mol), and lithium ethoxide (2 mL, 2 mmol) in THF (30 mL) were mixed and refluxed overnight. Pure **17** was obtained after column chromatography (100% dichloride methane on 60−200-mesh silica gel) to give 2.7 g. Yield: 19.2%. mp 175.5−177.6 °C. $^1$H NMR: $\delta$ 2.340 (s, 3H, Me), 2.124 (t, 3H, Me, coupled with F). $^{19}$F NMR: −138.048 (m, 2F), −148.058 (m, 1F), −158.890 (m, 2F). $^{13}$C NMR: 177.895, 174.651, 145.996 (2C), 143.004, 138.601 (2C), 110.327, 109.800, 108.618, 107.992, 106.275, 97.567, 61.044, 24.986, 14.363. Purity by HPLC, $\lambda = 300$ nm, 100%.

**2-Dicyanomethylene-3-cyano-4-methyl-5-phenyl-5-perfluoromethyl-2,5-dihydrofuran (18).** Compound **6** (10.0 g, 0.046 mol), malononitrile (6.1 g, 0.092 mol), lithium ethoxide (2.5 mL, 2.5 mmol), and THF (20 mL) were mixed and refluxed overnight. Pure **18** was obtained through column chromatography (100% dichloromethane on 60−200-mesh silica gel) to give 3.75 g. Yield: 25.9%. mp 133−135 °C. $^1$H NMR: 7.577−7.546 (m, 3H, Ar), 7.444−7.410 (m, 2H, Ar), 2.479 (s, 3H, Me). $^{19}$F NMR: −72.852. GC/MS: 317 (M + 2), 247 (M − $CF_3$). $^{13}$C NMR: 174.224, 172.148, 131.908, 130.191, 127.467, 125.742, 121.682, 109.793, 109.511, 109.098, 108.099, 98.521, 62.938, 15.439. Purity by HPLC, $\lambda = 320$ nm, 100%.

**2-Dicyanomethylene-3-cyano-4,5-dimethyl-5-[4′-cyclohexylphenyl]-2,5-dihydrofuran (19).** Compound **7** (40 g, 0.16 mol), malononitrile (21.1 g, 0.34 mol), lithium ethoxidel (5 mL, 0.005 mol, 1 M solution in ethanol), and THF (100 mL) were reacted and refluxed overnight. Pure **19** was obtained from recrystallization in ethanol to give 36 g. Yield: 71.2%. mp 194.2−195.5 °C. $^1$H NMR: $\delta$ 7.301 (d, 2H), 7.123 (d, 2H), 2.231 (s, 3H, Me), 1.996 (s, 3H, Me), 1.8−1.3 (m, 11H). $^{13}$C NMR: 182.319, 175.764, 151.127, 131.339, 128.359 (2C), 125.284 (2C), 111.021, 110.460, 109.186, 104.981, 101.776, 59.251, 44.450, 34.415 (2C), 26.917 (2C), 26.196, 22.606, 14.734. Purity by HPLC, $\lambda = 300$ nm, 100%.

**2-Dicyanomethylene-3-cyano-4,5-dimethyl-5-[4′-*n*-butylphenyl]-2,5-dihydrofuran (20).** Compound **8** (10.0 g, 0.0455 mol), malononitrile (6.0 g, 0.091 mol), lithium ethoxide (2.3 mL, 2.3 mmol). and THF (50 mL) were mixed and boiled at reflux overnight. Pure **20** was obtained from recrystallization in ethanol to give 9.95 g. Yield: 69.1%. mp 129.3−130.5 °C. $\delta$ $^1$H NMR: 7.259 (d, 2H), 7.112 (d, 2H), 2.638 (t, 2H, $CH_2$), 2.225 (s, 3H, Me), 1.997 (s, 3H, Me), 1.60−1.28 (m, 4H, $CH_2$), 0.931 (t, 3H, $CH_3$). $^{13}$C NMR: 182.476, 175.753, 145.841, 131.069, 129.692 (2C), 125.075 (2C), 110.914, 110.406, 109.088, 104.728, 101.724, 58.830, 35.236, 33.277, 22.335 (2C), 14.558, 13.873. Purity by HPLC, $\lambda = 240$ nm, 100%.

**2-Dicyanomethylene-3-cyano-4-methyl-5-spiro-cyclohexyl-2,5-dihydrofuran (21).** Compound **9** (14.2 g, 0.1 mol), malononitrile (13.2 g, 0.2 mol), sodium ethoxide (100 mL, 0.1 mol, 1 M solution in ethanol), and ethanol (100 mL) were mixed and reacted overnight at room temperature. Pure **21** was obtained from crystallization in ethanol to give 16.1 g. Yield: 67.5%. mp 236.5−237.5 °C. $^1$H NMR: $\delta$ 2.337 (s, 3H, Me), 1.86−1.70 (m, 11H, ring). $^{13}$C NMR: 182.387, 175.230, 110.980, 110.458, 108.999, 104.883, 101.437, 58.572, 33.123 (2C), 23.918, 21.289 (2C), 14.499. Purity by HPLC, $\lambda = 300$ nm, 100%.

**2-Dicyanomethylene-3-cyano-4-methyl-5-spiro-fluorenylidine-2,5-dihydrofuran (22).** Compound **10** (5.0 g, 0.0223 mol), malononitrile (2.94 g, 0.0446 mol), anhydrous potassium carbonate (3.1 g, 0.0223 mol), 18-crown-6 ether (catalytic amount), and dry THF (50 mL) were mixed and refluxed overnight. The pure **22** was collected by crystallization from ethanol to give 3.22 g. Yield: 45.0%. mp 302−303 °C. $^1$HNMR: $\delta$ 7.760 (d, 2H), 7.566 (t, 2H), 7.393 (t, 2H), 7.187 (d, 2H), 1.935 (s, 3H). $^{13}$C NMR: 177.504, 140.459, 136.594, 131.843, 128.818, 124.933, 121.099, 111.197, 110.621, 110.341, 109.205, 107.523, 104.207, 57.161, 12.793. Purity by HPLC, $\lambda = 300$ nm, 100%.

**2-Dicyanomethylene-3-cyano-4-methyl-5-spiro-[7-(1′,1′,2′,2′,3′,3′,4′,4′,4′-perfluorobutyl)tetralin]-2,5-dihydrofuran (23).** Compound **11** (6.8 g, 0.0167 mol), malononitrile (2.2 g, 0.033 mol), lithium ethoxide (1 mL, 1 mmol, 1 M solution in ethanol), and THF (20 mL) were reacted and refluxed overnight. Pure **23** was obtained by crystallization from ethanol to give 1 g. Yield: 11.86%. mp 211.0−212.4 °C. $^1$H NMR: 7.636 (dd, 1H), 7.479 (d, 1H), 6.925 (d, 1H), 3.148−2.879 (m, 2H), 2.252 (s, 3H, Me), 2.166 (m, 4H). $^{13}$C NMR: 178.962, 173.437, 142.286, 130.305, 128.206, 127.779, 127.473, 124.453, 118.514, 116.378, 114.119 (2C), 109.570, 109.105 (2C), 107.892, 107.830, 106.571, 98.558, 58.921, 32.632, 27.877, 17.537, 13.797. $^{19}$F NMR: −111.843 (2F), −123.282 (2F), and −126.127 (3F). Purity by HPLC, $\lambda = 330$ nm, 100%.

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**Supporting Information Available:** General experimental data: GC/MS analyses of compounds **1**−**12** and the HPLC analyses of compounds **14**−**23** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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